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(54) Title: PROSTATE CANCER EXPRESSION PROFILES

(57) Abstract: The present invention relates to all facets of novel polynucleotides, the polypeptides they encode, antibodies and specific binding partners thereto, and their applications to research, diagnosis, drub discovery, therapy, clinical medicine, forensic science and medicine, etc. The polynucleotides are differentially-regulated in prostate cancer and are therefore useful in variety of ways, including, but not limited to, as molecular markers, as drug targets, and for detecting, diagnosing, staging, monitoring, prognosticating, preventing or treating, determining predisposition to, etc., diseases and conditions, to prostate cancer.





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## PROSTATE CANCER EXPRESSION PROFILES

This application claims the benefit U.S. Provisional Application No. 60/281,731, filed April 6, 2001, and U.S. Provisional Application No. 60/281,732, filed April 6, 2001, which are hereby incorporated by reference in their entirety.

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## **DESCRIPTION OF THE DRAWINGS**

Tables 1 and 2 list genes differentially-regulated in prostate cancer. "DNA SEQ ID" and "Prt SEQ ID" refer to the corresponding DNA and protein sequences in the attached sequence listing. The genes can alternatively be referred to by GenBank accession number in the fifth column ("GI#") or the "identifier" in the third column. The genes listed in Table 1 are up-regulated, and those in Table 2 are down-regulated ("Exp" refers to the expression profile, U is up-regulated expression, and D is down-regulated expression). The characterization of the gene under the "description" heading is based on its listing in GenBank. 5', 3', genomic sequences, etc., which correspond to the genes can be retrieved routinely from Genbank, e.g., by searching the accession number. SEQ ID NOS 1-107 are DNA, and 108-211 are polypeptide. These sequences, and all information referenced to the accession number, are incorporated by reference in their entirety.

The polypeptide sequences was analyzed for the presence of functional domains using the publicly available Pfam program. This information is summarized in Table 3. Domains present in each polypeptide are listed under "domain." Any abbreviations are those used in Pfam. The start of the domain is indicated by "seq-f" and the end of the domain by "seq-t." The "score" is the statistical score of this match to the domain in bits. In general, a higher score indicates a better match. "E" is the statistical score of this match in Evalue (frequentist) approach. The smaller score in this case shows a better match between the domain and the query sequence. For more information on the program and scoring, see, e.g., Sonnhammer et al., *Proteins: Structure, Function and Genetics* 28:405-420 (1997); Sonnhammer et al., *Nucleic Acids Research*, 26:320-322 (1998); Bateman et al., *Nucleic Acids Research*, 27:260-262 (1999); Bateman et al., *Nucleic Acids Research*, 28:263-266 (2000).

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## **DESCRIPTION OF THE INVENTION**

The present invention relates to all facets of novel polynucleotides, the polypeptides they encode, antibodies and specific binding partners thereto, and their applications to research, diagnosis, drug discovery, therapy, clinical medicine, forensic science and medicine, etc. The polynucleotides are differentially regulated in prostate cancer and are therefore useful in variety of ways, including, but not limited to, as molecular markers, as drug targets, and for detecting, diagnosing, staging, monitoring, prognosticating, preventing or treating, determining predisposition to, etc., diseases and conditions,, especially relating to prostate cancer. The identification of specific genes, and groups of genes, expressed in pathways physiologically relevant to prostate cancer permits the definition of functional and disease pathways, and the delineation of targets in these pathways which are useful in diagnostic, therapeutic, and clinical applications. The present invention also relates to methods of using the polynucleotides and related products (proteins, antibodies, etc.) in business and computer-related methods, e.g., advertising, displaying, offering, selling, etc., such products for sale, commercial use, licensing, etc.

Prostate cancer is the most common form of cancer diagnosed in the American male, occurring predominantly in males over age 50. The number of men diagnosed with prostate cancer has steadily increased as a result of the increasing population of older men. The American Cancer Society estimates that in the year 2000, about 180,000 American men were diagnosed with prostate cancer and about 32,000 died from the disease. In comparison, 1998 estimates for lung cancer in men were 171,500 cases and 160,100 deaths, and for colorectal cancer, the estimates were 131,600 cases and 56,000 deaths. Despite these high numbers, 89 percent of men diagnosed with the disease will survive at least five years and 63 percent will survive at least 10 years.

Patients having prostate cancer display a wide range of phenotypes. In some men, following detection, the tumor remains a latent histological tumor and does not become clinically significant. However, in other men, the tumor progresses rapidly, metastasizing and killing the patient in a relatively short time. Prostate cancer can be cured if the tumor is confined to a small region of the gland and is discovered at early stage. In such cases, radiation or surgical removal often results in complete elimination of the disease. Frequently, however, the prostate cancer has already spread to surrounding tissue and metastasized to

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remote locations. In these cases, radiation and other therapies, are less likely to effect a complete cure.

Androgen deprivation is a conventional therapy to treat prostate cancer. Androgen blockade can be achieved through several different routes. Androgen suppressive drugs include, e.g., Lupron (leuprolide acetate), Casodex (bicalutamide), Eulexin (flutamide), Nilandron (nilutamide), Zoladex (goserelin acetate implant), and Viadur (leuprolide acetate), which act through several different mechanisms. While these drugs may offer remission and tumor regression in many cases, often the therapeutic effects are only temporary. Prostate tumors lose their sensitivity to such treatments, and become androgen-independent. Thus, new therapies are clearly needed.

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The first clinical symptoms of prostate cancer are typically urinary disturbances, including painful and more frequent urination. Diagnosis for prostate cancer is usually accomplished using a combination of different procedures. Since the prostate is located next to the rectum, rectal digital examination allows the prostate to be examined manually for the presence of hyperplasia and abnormal tissue masses. Usually, this is the first line of detection. If a palpable mass is observed, a blood specimen can be assayed for prostate-specific antigen (PSA). Very little PSA is present in the blood of a healthy individual, but BPH and prostate cancer can cause large amounts of PSA to be released into the blood, indicating the presence of diseased tissue. Definitive diagnosis is generally accomplished by biopsy of the prostate tissue.

No single gene or protein has been identified which is responsible for the etiology of all prostate cancers. Although PSA is widely used as a diagnostic reagent, it has limitations in its sensitivity and its ability to detect early cancers. It is estimated that approximately 20% to 30% of tumors will be missed when PSA is used alone. It is likely that diagnostic and prognostic markers for prostate cancer disease will involve the identification and use of many different genes and gene products to reflect its multifactorial origin.

A continuing goal is to characterize the gene expression patterns of the various prostate cancers to genetically differentiate them, providing important guidance in preventing and treating cancers. Molecular pictures of cancer, such as the pattern of differentially-regulated genes identified herein, provide an important tool for molecularly dissecting and classifying cancer, identifying drug targets, providing prognosis and therapeutic information, etc. For instance, an array of polynucleotides corresponding to genes differentially regulated in prostate cancer can be used to screen tissue samples for the existence of cancer, to

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categorize the cancer (e.g., by the particular pattern observed), to grade the cancer (e.g., by the number of differentially-regulated genes and their amounts of expression), to identify the source of a secondary tumor, to screen for metastatic cells, etc. These arrays can be used in combination with other markers, e.g., PSA, PMSA (prostate membrane specific antigen), or

5 any of the grading systems used in clinical medicine.

As indicated by these studies, cancer is a highly diverse disease. Although all cancers share certain characteristics, the underlying cause and disease progression can differ significantly from patient to patient. So far, over a dozen distinct genes have been identified which, when mutant, result in a cancer. In breast cancer, alone, a handful of different genes have been isolated which either cause the cancer, or produce a predisposition to it. As a consequence, disease phenotypes for a particular cancer do not look all the same. In addition to the differences in the gene(s) responsible for the cancer, heterogeneity among individuals, e.g., in age, health, sex, and genetic background, can also influence the disease and its progression. Gene penetrance, in particular, can vary widely among population members. Recent studies have shown tremendous diversity in gene expression patterns among cancer patients. For these and other reasons, one gene/polypeptide target alone can be insufficient to diagnose or treat a cancer. Even a gene which is highly differentially-expressed and penetrant in cancer patients may not be so highly expressed in all patients and at all stages of the cancer. By selecting a set of genes and/or the polypeptides they encode, cancer diagnostics and therapeutics can be designed which effectively diagnose and treat a population of diseased individuals, rather than only a small handful when single genes are targeted.

## Nucleic acids

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In accordance with the present invention, genes have been identified which are differentially expressed in prostate cancer. Tables 1 and 2 list of genes which are differentially-regulated in the cancer. These genes can be further divided into groups based on additional characteristics of their expression and the tissues in which they are expressed. For instance, genes can be further subdivided based on the stage and/or grade of the cancer in which they are expressed. Genes can also be grouped based on their penetrance in a prostate cancer, e.g., expressed in all prostate cancer examined, expressed in a certain percentage of prostate cancer examined, etc. Additionally, genes can be categorized by their function and/or the polypeptides they encode. This includes, but is not limited to, cellular

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localization, functional activity (e.g., kinase, cytoskeletal element, or transcriptional factor), functional pathway (e.g., protein manufacture, cell signaling, cell movement, cell adhesion, responsivity to cAMP, energy production, etc.), etc. These groupings do not restrict or limit the use such genes in therapeutic, diagnostic, prognostic, etc., applications. For instance, a gene which is expressed in only some cancers (e.g., incompletely penetrant) may be useful in therapeutic applications to treat a subset of cancers. Similarly, a co-penetrant gene, or a gene which is expressed in prostate cancer and other normal tissues, may be useful as a therapeutic or diagnostic, even if its expression pattern is not highly prostate specific. Thus, the uses of the genes or their products are not limited by their patterns of expression.

For genes which are differentially-regulated, gene and protein replacement therapies can be used therapeutically to restore expression levels to normal. When a protein product is to be administered, secreted proteins are more likely to be targets for replacement therapy than intracellular and membrane-bound proteins. For the latter classes, gene therapy may be a more effective means of delivery, e.g., administering a gene which is expressed inside a cell on or on its surface.

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By the phrase "differential expression," it is meant that the levels of expression of a gene, as measured by its transcription or translation product, are different depending upon the specific cell-type or tissue (e.g., in an averaging assay that looks at a population of cells). There are no absolute amounts by which the gene expression levels must vary, as long as the differences are measurable.

The phrase "down-regulated" indicates that an mRNA transcript or other nucleic acid corresponding to a polynucleotide of the present invention is expressed in lower amounts in a cancer as compared to the same transcript expressed in normal cells from which the cancer was derived. In general, down-regulation can be assessed by any suitable method, including any of the nucleic acid detection and hybridization methods mentioned below, as well as polypeptide-based methods. Down-regulation also includes going from substantially no expression in a normal tissue, from detectable expression in a normal tissue, from significant expression in a normal tissue, to higher levels in the cancer.

The phrase "up-regulated" indicates that an mRNA transcript or other nucleic acid corresponding to a polynucleotide of the present invention is expressed in larger amounts in a cancer as compared to the same transcript expressed in normal cells from which the cancer was derived. For instance, a gene's up-regulation can be determined by comparing its abundance per gram of RNA (e.g., total RNA, polyadenylated mRNA, etc.) extracted from a

cancer tissue in comparison to the corresponding normal tissue. The normal tissue can be from the same or different individual or source. For convenience, it can be supplied as a separate component or in a kit in combination with probes and other reagents for detecting genes. The quantity by which a nucleic acid is up-regulated can be any value, e.g., more than 10%, 50%, 2-fold, 5-fold, 10-fold, etc. Up-regulation also includes going from substantially no expression, to detectable expression, to significant or highly restricted expression, etc.

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Differential regulation can be determined by any suitable method, e.g., by comparing its abundance per gram of RNA (e.g., total RNA, polyadenylated mRNA, etc.) extracted from a prostate tissue in comparison to the corresponding normal tissue. The normal tissue can be from the same or different individual or source. For convenience, it can be supplied as a separate component or in a kit in combination with probes and other reagents for detecting genes. The quantity by which a nucleic acid is differentially-regulated can be any value, e.g., about 10% more or less of normal expression, about 50% more or less of normal expression, 2-fold more or less, 5-fold more or less, 10-fold more or less, etc.

The amount of transcript can also be compared to a different gene in the same sample, especially a gene whose abundance is known and substantially no different in its expression between normal and cancer cells (e.g., a "control" gene). If represented as a ratio, with the quantity of differentially-regulated gene transcript in the numerator and the control gene transcript in the denominator, the ratio would be larger, e.g., in breast cancer than in a sample from normal breast tissue.

Differential-regulation can arise through a number of different mechanisms. The present invention is not bound by any specific way through which it occurs. Differential-regulation of a polynucleotide can occur, e.g., by modulating (1) transcriptional rate of the gene (e.g., increasing its rate, inducing or stimulating its transcription from a basal, low-level rate, etc.), (2) the post-transcriptional processing of RNA transcripts, (3) the transport of RNA from the nucleus into the cytoplasm, (4) RNA nuclear and cytoplasmic turnover and polypeptide turnover (e.g., by virtue of having higher stability or resistance to degradation), and combinations thereof. See, e.g., Tollervey and Caceras, *Cell*, 103:703-709, 2000.

A differentially-regulated polynucleotide is useful in a variety of different applications as described in greater details below. Because it is more abundant in cancer, it and its expression products can be used in a diagnostic test to assay for the presence of cancer, e.g., in tissue sections, in a biopsy sample, in total RNA, in lymph, in blood, etc. Differentially-regulated polynucleotides and polypeptides can be used individually, or in

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groups, to assess the cancer, e.g., to determine the specific type of cancer, its stage of development, the nature of the genetic defect, etc., or to assess the efficacy of a treatment modality. How to use polynucleotides in diagnostic and prognostic assays is discussed below. In addition, the polynucleotides and the polypeptides they encode, can serve as a target for therapy or drug discovery. A polypeptide, coded for by a differentially-regulated polynucleotide, which is displayed on the cell-surface, can be a target for immunotherapy to destroy, inhibit, etc., the diseased tissue. Differentially-regulated transcripts can also be used in drug discovery schemes to identify pharmacological agents which suppress, inhibit, etc., their differential-regulation, thereby preventing the phenotype associated with their expression. Thus, a differentially-regulated polynucleotide and its expression products of the present invention have significant applications in diagnostic, therapeutic, prognostic, drug development, and related areas.

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The expression patterns of the differentially expressed genes disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by a cancer. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of genes represented in Tables 1 and 2 provide an example of a cell expression profile for a prostate cancer. It can be used as a point of reference to compare and characterize unknown samples and samples for which further information is sought. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue as being a prostate cancer, to determine the origin of a particular cancer (e.g., the origin of metastatic cells), to determine the presence of a cancer in a biopsy sample, to assess the efficacy of a cancer therapy in a human patient or a non-human animal model, to detect circulating cancer cells in blood or a lymph node biopsy, etc. While the expression profile of the complete gene set represented in Tables 1 and 2 may be most informative, a fingerprint containing expression information from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, cancer is a multifactorial disease, involving genetic aberrations in more than gene locus. This multifaceted nature may be reflected in different cell expression profiles associated with breast cancers arising in different individuals, in different locations in the same individual, or even within the same cancer locus. As a result, a complete match with a particular cell expression profile, as

shown herein, is not necessary to classify a cancer as being of the same type or stage. Similarity to one cell expression profile, e.g., as compared to another, can be adequate to classify cancer types, grades, and stages. SEQ ID NOS 1-211 are referred to generally as "genes" to indicate that they represent specific gene loci, and are not limited to the particular nucleotide and polypeptide sequences disclosed herein. For example, fibronectin (SEQ ID NO 60 and 196) is up-regulated in prostate cancers. Probes to detect its up regulation can be selected from the attached specific sequences, as well as genomic, upstream, downstream, and intron sequences which are not in the attached sequence listing.

A mammalian polynucleotide, or fragment thereof, of the present invention is a polynucleotide having a nucleotide sequence obtainable from a natural source. It therefore includes naturally-occurring normal, naturally-occurring mutant, and naturally-occurring polymorphic alleles (e.g., SNPs), differentially-spliced transcripts, splice-variants, etc. By the term "naturally-occurring," it is meant that the polynucleotide is obtainable from a natural source, e.g., animal tissue and cells, body fluids, tissue culture cells, forensic samples.

Natural sources include, e.g., living cells obtained from tissues and whole organisms, tumors, cultured cell lines, including primary and immortalized cell lines. Naturally-occurring mutations can include deletions (e.g., a truncated amino- or carboxy-terminus), substitutions, inversions, or additions of nucleotide sequence. These genes can be detected and isolated by polynucleotide hybridization according to methods which one skilled in the art would know, e.g., as discussed below.

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A polynucleotide according to the present invention can be obtained from a variety of different sources. It can be obtained from DNA or RNA, such as polyadenylated mRNA or total RNA, e.g., isolated from tissues, cells, or whole organism. The polynucleotide can be obtained directly from DNA or RNA, from a cDNA library, from a genomic library, etc. The polynucleotide can be obtained from a cell or tissue (e.g., from an embryonic or adult tissues) at a particular stage of development, having a desired genotype, phenotype, disease status, etc.

The genes described in Tables 1 and 2 can be partial sequences that correspond to full-length, naturally-occurring transcripts. The present invention includes, as well, full-length polynucleotides that comprise these partial sequences, e.g., genomic DNAs and polynucleotides comprising a start and stop codon, a start codon and a polyA tail, a transcription start and a polyA tail, etc. These sequences can be obtained by any suitable method, e.g., using a partial sequence as a probe to select a full-length cDNA from a library

containing full-length inserts. A polynucleotide which "codes without interruption" refers to a polynucleotide having a continuous open reading frame ("ORF") as compared to an ORF which is interrupted by introns or other noncoding sequences.

## 5 Genomic

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The present invention also relates genomic DNA from which the polynucleotides of the present invention can be derived. A genomic DNA coding for a human, mouse, or other mammalian polynucleotide, can be obtained routinely, for example, by screening a genomic library (e.g., a YAC library) with a polynucleotide of the present invention, or by searching nucleotide databases, such as GenBank and EMBL, for matches. Promoter and other regulatory regions can be identified upstream of coding and expressed RNAs, and assayed routinely for activity, e.g., by joining to a reporter gene (e.g., CAT, GFP, alkaline phosphatase, luciferase, galatosidase). A promoter obtained from a prostate selective gene can be used, e.g., in gene therapy to obtain tissue-specific expression of a heterologous gene (e.g., coding for a therapeutic product or cytotoxin).

#### Constructs

A polynucleotide of the present invention can comprise additional polynucleotide sequences, e.g., sequences to enhance expression, detection, uptake, cataloging, tagging, etc. A polynucleotide can include only coding sequence; a coding sequence and additional non-naturally occurring or heterologous coding sequence (e.g., sequences coding for leader, signal, secretory, targeting, enzymatic, fluorescent, antibiotic resistance, and other functional or diagnostic peptides); coding sequences and non-coding sequences, e.g., untranslated sequences at either a 5' or 3' end, or dispersed in the coding sequence, e.g., introns.

A polynucleotide according to the present invention also can comprise an expression control sequence operably linked to a polynucleotide as described above. The phrase "expression control sequence" means a polynucleotide sequence that regulates expression of a polypeptide coded for by a polynucleotide to which it is functionally ("operably") linked. Expression can be regulated at the level of the mRNA or polypeptide. Thus, the expression control sequence includes mRNA-related elements and protein-related elements. Such elements include promoters, enhancers (viral or cellular), ribosome binding sequences, transcriptional terminators, etc. An expression control sequence is operably linked to a nucleotide coding sequence when the expression control sequence is positioned in such a

manner to effect or achieve expression of the coding sequence. For example, when a promoter is operably linked 5' to a coding sequence, expression of the coding sequence is driven by the promoter. Expression control sequences can include an initiation codon and additional nucleotides to place a partial nucleotide sequence of the present invention in-frame in order to produce a polypeptide (e.g., pET vectors from Promega have been designed to permit a molecule to be inserted into all three reading frames to identify the one that results in polypeptide expression). Expression control sequences can be heterologous or endogenous to the normal gene.

A polynucleotide of the present invention can also comprise nucleic acid vector sequences, e.g., for cloning, expression, amplification, selection, etc. Any effective vector can be used. A vector is, e.g., a polynucleotide molecule which can replicate autonomously in a host cell, e.g., containing an origin of replication. Vectors can be useful to perform manipulations, to propagate, and/or obtain large quantities of the recombinant molecule in a desired host. A skilled worker can select a vector depending on the purpose desired, e.g., to propagate the recombinant molecule in bacteria, yeast, insect, or mammalian cells. The following vectors are provided by way of example. Bacterial: pQE70, pQE60, pQE-9 (Qiagen), pBS, pD10, Phagescript, phiX174, pBK Phagemid, pNH8A, pNH16a, pNH18Z, pNH46A (Stratagene); Bluescript KS+II (Stratagene); ptrc99a, pKK223-3, pKK233-3, pDR54 0, pRIT5 (Pharmacia). Eukaryotic: PWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene), pSVK3, PBPV, PMSG, pSVL (Pharmacia), pCR2.1/TOPO, pCRII/TOPO, pCR4/TOPO, pTrcHisB, pCMV6-XL4, etc. However, any other vector, e.g., plasmids, viruses, or parts thereof, may be used as long as they are replicable and viable in the desired host. The vector can also comprise sequences which enable it to replicate in the host whose genome is to be modified.

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## Hybridization

Polynucleotide hybridization, as discussed in more detail below, is useful in a variety of applications, including, in gene detection methods, for identifying mutations, for making mutations, to identify homologs in the same and different species, to identify related members of the same gene family, in diagnostic and prognostic assays, in therapeutic applications (e.g., where an antisense polynucleotide is used to inhibit expression), etc.

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The ability of two single-stranded polynucleotide preparations to hybridize together is a measure of their nucleotide sequence complementarity, e.g., base-pairing between nucleotides, such as A-T, G-C, etc. The invention thus also relates to polynucleotides, and their complements, which hybridize to a polynucleotide comprising a nucleotide sequence as set forth in Tables 1 and 2 and genomic sequences thereof. A nucleotide sequence hybridizing to the latter sequence will have a complementary polynucleotide strand, or act as a template for one in the presence of a polymerase (i.e., an appropriate polynucleotide synthesizing enzyme). The present invention includes both strands of polynucleotide, e.g., a sense strand and an anti-sense strand.

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Hybridization conditions can be chosen to select polynucleotides which have a desired amount of nucleotide complementarity with the nucleotide sequences set forth in Tables 1 and 2 and genomic sequences thereof. A polynucleotide capable of hybridizing to such sequence, preferably, possesses, e.g., about 70%, 75%, 80%, 85%, 87%, 90%, 92%, 95%, 97%, 99%, or 100% complementarity, between the sequences. The present invention particularly relates to polynucleotide sequences which hybridize to the nucleotide sequences set forth in Tables 1 and 2 or genomic sequences thereof, under low or high stringency conditions. These conditions can be used, e.g., to select corresponding homologs in non-human species.

Polynucleotides which hybridize to polynucleotides of the present invention can be selected in various ways. Filter-type blots (i.e., matrices containing polynucleotide, such as nitrocellulose), glass chips, and other matrices and substrates comprising polynucleotides (short or long) of interest, can be incubated in a prehybridization solution (e.g., 6X SSC, 0.5% SDS, 100 μg/ml denatured salmon sperm DNA, 5X Denhardt's solution, and 50% formamide), at 22-68°C, overnight, and then hybridized with a detectable polynucleotide probe under conditions appropriate to achieve the desired stringency. In general, when high homology or sequence identity is desired, a high temperature can be used (e.g., 65 °C). As the homology drops, lower washing temperatures are used. For salt concentrations, the lower the salt concentration, the higher the stringency. The length of the probe is another consideration. Very short probes (e.g., less than 100 base pairs) are washed at lower temperatures, even if the homology is high. With short probes, formamide can be omitted. See, e.g., *Current Protocols in Molecular Biology*, Chapter 6, Screening of Recombinant Libraries; Sambrook et al., *Molecular Cloning*, 1989, Chapter 9.

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For instance, high stringency conditions can be achieved by incubating the blot overnight (e.g., at least 12 hours) with a long polynucleotide probe in a hybridization solution containing, e.g., about 5X SSC, 0.5% SDS, 100 µg/ml denatured salmon sperm DNA and 50% formamide, at 42°C. Blots can be washed at high stringency conditions that allow, e.g., for less than 5% bp mismatch (e.g., wash twice in 0.1% SSC and 0.1% SDS for 30 min at 65°C), i.e., selecting sequences having 95% or greater sequence identity.

Other non-limiting examples of high stringency conditions includes a final wash at 65°C in aqueous buffer containing 30 mM NaCl and 0.5% SDS. Another example of high stringent conditions is hybridization in 7% SDS, 0.5 M NaPO<sub>4</sub>, pH 7, 1 mM EDTA at 50°C, e.g., overnight, followed by one or more washes with a 1% SDS solution at 42°C. Whereas high stringency washes can allow for less than 5% mismatch, reduced or low stringency conditions can permit up to 20% nucleotide mismatch. Hybridization at low stringency can be accomplished as above, but using lower formamide conditions, lower temperatures and/or lower salt concentrations, as well as longer periods of incubation time.

Hybridization can also be based on a calculation of melting temperature (Tm) of the hybrid formed between the probe and its target, as described in Sambrook et al..

Generally, the temperature Tm at which a short oligonucleotide (containing 18 nucleotides or fewer) will melt from its target sequence is given by the following equation: Tm = (number of A's and T's) x 2°C + (number of C's and G's) x 4°C. For longer molecules, Tm = 81.5 + 16.6 log<sub>10</sub>[Na<sup>+</sup>] + 0.41(%GC) - 600/N where [Na<sup>+</sup>] is the molar concentration of sodium ions, %GC is the percentage of GC base pairs in the probe, and N is the length. Hybridization can be carried out at several degrees below this temperature to ensure that the probe and target can hybridize. Mismatches can be allowed for by lowering the temperature even further.

Stringent conditions can be selected to isolate sequences, and their complements, which have, e.g., at least about 90%, 95%, or 97%, nucleotide complementarity between the probe (e.g., a short polynucleotide of Tables 1 and 2 or genomic sequences thereof) and a target polynucleotide.

Other homologs of polynucleotides of the present invention can be obtained from mammalian and non-mammalian sources according to various methods. For example, hybridization with a polynucleotide can be employed to select homologs, e.g., as described in Sambrook et al., *Molecular Cloning*, Chapter 11, 1989. Such homologs can have varying amounts of nucleotide and amino acid sequence identity and similarity to such

polynucleotides of the present invention. Mammalian organisms include, e.g., mice, rats, monkeys, pigs, cows, etc. Non-mammalian organisms include, e.g., vertebrates, invertebrates, zebra fish, chicken, Drosophila, C. elegans, Xenopus, yeast such as S. pombe, S. cerevisiae, roundworms, prokaryotes, plants, Arabidopsis, artemia, viruses, etc. The degree of nucleotide sequence identity between human and mouse can be about, e.g. 70% or more, 85% or more for open reading frames, etc.

## Alignment

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Alignments can be accomplished by using any effective algorithm. For pairwise alignments of DNA sequences, the methods described by Wilbur-Lipman (e.g., Wilbur and Lipman, Proc. Natl. Acad. Sci., 80:726-730, 1983) or Martinez/Needleman-Wunsch (e.g., Martinez, Nucleic Acid Res., 11:4629-4634, 1983) can be used. For instance, if the Martinez/Needleman-Wunsch DNA alignment is applied, the minimum match can be set at 9, gap penalty at 1.10, and gap length penalty at 0.33. The results can be calculated as a similarity index, equal to the sum of the matching residues divided by the sum of all residues and gap characters, and then multiplied by 100 to express as a percent. Similarity index for related genes at the nucleotide level in accordance with the present invention can be greater than 70%, 80%, 85%, 90%, 95%, 99%, or more. Pairs of protein sequences can be aligned by the Lipman-Pearson method (e.g., Lipman and Pearson, Science, 227:1435-1441, 1985) with k-tuple set at 2, gap penalty set at 4, and gap length penalty set at 12. Results can be expressed as percent similarity index, where related genes at the amino acid level in accordance with the present invention can be greater than 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more. Various commercial and free sources of alignment programs are available, e.g., MegAlign by DNA Star, BLAST (National Center for Biotechnology Information), BCM (Baylor College of Medicine) Launcher, etc.

Percent sequence identity can also be determined by other conventional methods, e.g., as described in Altschul et al., *Bull. Math. Bio.* 48: 603-616, 1986 and Henikoff and Henikoff, *Proc. Natl. Acad. Sci.* USA 89:10915-10919, 1992.

## 30 Specific polynucleotide probes

A polynucleotide of the present invention can comprise any continuous nucleotide sequence of Tables 1 and 2, sequences which share sequence identity thereto, or complements thereof. The term "probe" refers to any substance that can be used to detect,

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identify, isolate, etc., another substance. A polynucleotide probe is comprised of nucleic acid can be used to detect, identify, etc., other nucleic acids, such as DNA and RNA.

These polynucleotides can be of any desired size that is effective to achieve the specificity desired. For example, a probe can be from about 7 or 8 nucleotides to several thousand nucleotides, depending upon its use and purpose. For instance, a probe used as a primer PCR can be shorter than a probe used in an ordered array of polynucleotide probes. Probe sizes vary, and the invention is not limited in any way by their size, e.g., probes can be from about 7-2000 nucleotides, 7-1000, 8-700, 8-600, 8-500, 8-400, 8-300, 8-150, 8-100, 8-75, 7-50, 10-25, 14-16, at least about 8, at least about 10, at least about 15, at least about 25, etc. The polynucleotides can have non-naturally-occurring nucleotides, e.g., inosine, AZT, 3TC, etc. The polynucleotides can have 100% sequence identity or complementarity to a sequence of Tables 1 and 2, or it can have mismatches or nucleotide substitutions, e.g., 1, 2, 3, 4, or 5 substitutions. The probes can be single-stranded or double-stranded.

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In accordance with the present invention, a polynucleotide can be present in a kit, where the kit includes, e.g., one or more polynucleotides, a desired buffer (e.g., phosphate, tris, etc.), detection compositions, RNA or cDNA from different tissues to be used as controls, libraries, etc. The polynucleotide can be labeled or unlabeled, with radioactive or non-radioactive labels as known in the art. Kits can comprise one or more pairs of polynucleotides for amplifying nucleic acids specific for differentially-regulated genes of the present invention, e.g., comprising a forward and reverse primer effective in PCR. These include both sense and anti-sense orientations. For instance, in PCR-based methods (such as RT-PCR), a pair of primers are typically used, one having a sense sequence and the other having an antisense sequence.

Another aspect of the present invention is a nucleotide sequence that is specific to, or for, a selective polynucleotide. The phrases "specific for" or "specific to" a polynucleotide have a functional meaning that the polynucleotide can be used to identify the presence of one or more target genes in a sample. It is specific in the sense that it can be used to detect polynucleotides above background noise ("non-specific binding"). A specific sequence is a defined order of nucleotides which occurs in the polynucleotide, e.g., in the nucleotide sequences of Tables 1 and 2. A probe or mixture of probes can comprise a sequence or sequences that are specific to a plurality of target sequences, e.g., where the sequence is a consensus sequence, a functional domain, etc., e.g., capable of recognizing a family of related genes. Such sequences can be used as probes in any of the methods described herein or

incorporated by reference. Both sense and antisense nucleotide sequences are included. A specific polynucleotide according to the present invention can be determined routinely.

A polynucleotide comprising a specific sequence can be used as a hybridization probe to identify the presence of, e.g., human or mouse polynucleotide, in a sample comprising a mixture of polynucleotides, e.g., on a Northern blot. Hybridization can be performed under high stringent conditions (see, above) to select polynucleotides (and their complements which can contain the coding sequence) having at least 90%, 95%, 99%, etc., identity (i.e., complementarity) to the probe, but less stringent conditions can also be used. A specific polynucleotide sequence can also be fused in-frame, at either its 5' or 3' end, to various nucleotide sequences as mentioned throughout the patent, including coding sequences for enzymes, detectable markers, GFP, etc, expression control sequences, etc.

A polynucleotide probe, especially one that is specific to a polynucleotide of the present invention, can be used in gene detection and hybridization methods as already described. In one embodiment, a specific polynucleotide probe can be used to detect whether a particular tissue or cell-type is present in a target sample. To carry out such a method, a selective polynucleotide can be chosen which is characteristic of the desired target tissue. Such polynucleotide is preferably chosen so that it is expressed or displayed in the target tissue, but not in other tissues which are present in the sample. For instance, if detection of prostate is desired, it may not matter whether the selective polynucleotide is expressed in other tissues, as long as it is not expressed in cells normally present in blood, e.g., peripheral blood mononuclear cells. Starting from the selective polynucleotide, a specific polynucleotide probe can be designed which hybridizes (if hybridization is the basis of the assay) under the hybridization conditions to the selective polynucleotide, whereby the presence of the selective polynucleotide can be determined.

Probes which are specific for polynucleotides of the present invention can also be prepared using involve transcription-based systems, e.g., incorporating an RNA polymerase promoter into a selective polynucleotide of the present invention, and then transcribing antisense RNA using the polynucleotide as a template. See, e.g., U.S. Pat. No. 5,545,522.

#### Polynucleotide composition

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A polynucleotide according to the present invention can comprise, e.g., DNA, RNA, synthetic polynucleotide, peptide polynucleotide, modified nucleotides, dsDNA, ssDNA, ssRNA, dsRNA, and mixtures thereof. A polynucleotide can be single- or double-stranded,

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triplex, DNA:RNA, duplexes, comprise hairpins, and other secondary structures, etc. Nucleotides comprising a polynucleotide can be joined via various known linkages, e.g., ester, sulfamate, sulfamide, phosphorothioate, phosphoramidate, methylphosphonate, carbamate, etc., depending on the desired purpose, e.g., resistance to nucleases, such as RNAse H, improved in vivo stability, etc. See, e.g., U.S. Pat. No. 5,378,825. Any desired nucleotide or nucleotide analog can be incorporated, e.g., 6-mercaptoguanine, 8-oxo-guanine, etc.

Various modifications can be made to the polynucleotides, such as attaching detectable markers (avidin, biotin, radioactive elements, fluorescent tags and dyes, energy transfer labels, energy-emitting labels, binding partners, etc.) or moieties which improve hybridization, detection, and/or stability. The polynucleotides can also be attached to solid supports, e.g., nitrocellulose, magnetic or paramagnetic microspheres (e.g., as described in U.S. Pat. No. 5,411,863; U.S. Pat. No. 5,543,289; for instance, comprising ferromagnetic, supermagnetic, paramagnetic, superparamagnetic, iron oxide and polysaccharide), nylon, agarose, diazotized cellulose, latex solid microspheres, polyacrylamides, etc., according to a desired method. See, e.g., U.S. Pat. Nos. 5,470,967, 5,476,925, and 5,478,893.

Polynucleotide according to the present invention can be labeled according to any desired method. The polynucleotide can be labeled using radioactive tracers such as <sup>32</sup>P, <sup>35</sup>S, <sup>3</sup>H, or <sup>14</sup>C, to mention some commonly used tracers. The radioactive labeling can be carried out according to any method, such as, for example, terminal labeling at the 3' or 5' end using a radiolabeled nucleotide, polynucleotide kinase (with or without dephosphorylation with a phosphatase) or a ligase (depending on the end to be labeled). A non-radioactive labeling can also be used, combining a polynucleotide of the present invention with residues having immunological properties (antigens, haptens), a specific affinity for certain reagents (ligands), properties enabling detectable enzyme reactions to be completed (enzymes or coenzymes, enzyme substrates, or other substances involved in an enzymatic reaction), or characteristic physical properties, such as fluorescence or the emission or absorption of light at a desired wavelength, etc.

#### Nucleic acid detection methods

Another aspect of the present invention relates to methods and processes for detecting differentially-regulated genes of the present invention. Detection methods have a variety of applications, including for diagnostic, prognostic, forensic, and research applications. To

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accomplish gene detection, a polynucleotide in accordance with the present invention can be used as a "probe." The term "probe" or "polynucleotide probe" has its customary meaning in the art, e.g., a polynucleotide which is effective to identify (e.g., by hybridization), when used in an appropriate process, the presence of a target polynucleotide to which it is designed. Identification can involve simply determining presence or absence, or it can be quantitative, e.g., in assessing amounts of a gene or gene transcript present in a sample. Probes can be useful in a variety of ways, such as for diagnostic purposes, to identify homologs, and to detect, quantitate, or isolate a polynucleotide of the present invention in a test sample.

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Assays can be utilized which permit quantification and/or presence/absence detection of a target nucleic acid in a sample. Assays can be performed at the single-cell level, or in a sample comprising many cells, where the assay is "averaging" expression over the entire collection of cells and tissue present in the sample. Any suitable assay format can be used, including, but not limited to, e.g., Southern blot analysis, Northern blot analysis, polymerase chain reaction ("PCR") (e.g., Saiki et al., Science, 241:53, 1988; U.S. Pat. Nos. 4,683,195, 4,683,202, and 6,040,166; PCR Protocols: A Guide to Methods and Applications, Innis et al., eds., Academic Press, New York, 1990), reverse transcriptase polymerase chain reaction ("RT-PCR"), anchored PCR, rapid amplification of cDNA ends ("RACE") (e.g., Schaefer in Gene Cloning and Analysis: Current Innovations, Pages 99-115, 1997), ligase chain reaction ("LCR") (EP 320 308), one-sided PCR (Ohara et al., Proc. Natl. Acad. Sci., 86:5673-5677, 1989), indexing methods (e.g., U.S. Pat. No. 5,508,169), in situ hybridization, differential display (e.g., Liang et al., Nucl. Acid. Res., 21:3269-3275, 1993; U.S. Pat. Nos. 5,262,311, 5,599,672 and 5,965,409; WO97/18454; Prashar and Weissman, Proc. Natl. Acad. Sci., 93:659-663, and U.S. Pat. Nos. 6,010,850 and 5,712,126; Welsh et al., Nucleic Acid Res., 20:4965-4970, 1992, and U.S. Pat. No. 5,487,985) and other RNA fingerprinting techniques, nucleic acid sequence based amplification ("NASBA") and other transcription based amplification systems (e.g., U.S. Pat. Nos. 5,409,818 and 5,554,527; WO 88/10315), polynucleotide arrays (e.g., U.S. Pat. Nos. 5,143,854, 5,424,186; 5,700,637, 5,874,219, and 6,054,270; PCT WO 92/10092; PCT WO 90/15070), Qbeta Replicase (PCT/US87/00880), Strand Displacement Amplification ("SDA"), Repair Chain Reaction ("RCR"), nuclease protection assays, subtraction-based methods, Rapid-Scan™, etc. Additional useful methods include, but are not limited to, e.g., template-based amplification methods, competitive PCR (e.g., U.S. Pat. No. 5,747,251), redox-based assays (e.g., U.S. Pat. No. 5,871,918), Taqmanbased assays (e.g., Holland et al., Proc. Natl. Acad, Sci., 88:7276-7280, 1991; U.S. Pat. Nos.

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5,210,015 and 5,994,063), real-time fluorescence-based monitoring (e.g., U.S. Pat. 5,928,907), molecular energy transfer labels (e.g., U.S. Pat. Nos. 5,348,853, 5,532,129, 5,565,322, 6,030,787, and 6,117,635; Tyagi and Kramer, *Nature Biotech.*, 14:303-309, 1996). Any method suitable for single cell analysis of gene or protein expression can be used, including in situ hybridization, immunocytochemistry, MACS, FACS, flow cytometry, etc. For single cell assays, expression products can be measured using antibodies, PCR, or other types of nucleic acid amplification (e.g., Brady et al., *Methods Mol. & Cell. Biol.* 2, 17-25, 1990; Eberwine et al., 1992, *Proc. Natl. Acad. Sci.*, 89, 3010-3014, 1992; U.S. Pat. No. 5,723,290). These and other methods can be carried out conventionally, e.g., as described in the mentioned publications.

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Many of such methods may require that the polynucleotide is labeled, or comprises a particular nucleotide type useful for detection. The present invention includes such modified polynucleotides that are necessary to carry out such methods. Thus, polynucleotides can be DNA, RNA, DNA:RNA hybrids, PNA, etc., and can comprise any modification or substituent which is effective to achieve detection.

Detection can be desirable for a variety of different purposes, including research, diagnostic, prognostic, and forensic. For diagnostic purposes, it may be desirable to identify the presence or quantity of a polynucleotide sequence in a sample, where the sample is obtained from tissue, cells, body fluids, etc. In a preferred method as described in more detail below, the present invention relates to a method of detecting a polynucleotide comprising, contacting a target polynucleotide in a test sample with a polynucleotide probe under conditions effective to achieve hybridization between the target and probe; and detecting hybridization.

Any test sample in which it is desired to identify a polynucleotide or polypeptide thereof can be used, including, e.g., blood, urine, saliva, stool (for extracting nucleic acid, see, e.g., U.S. Pat. No. 6,177,251), swabs comprising tissue, biopsied tissue, tissue sections, cultured cells, etc.

Detection can be accomplished in combination with polynucleotide probes for other genes, e.g., genes which are expressed in other disease states, tissues, cells, such as brain, heart, kidney, spleen, thymus, liver, stomach, small intestine, colon, muscle, lung, testis, placenta, pituitary, thyroid, skin, adrenal gland, pancreas, salivary gland, uterus, ovary, prostate gland, peripheral blood cells (T-cells, lymphocytes, etc.), embryo, normal breast fat,

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adult and embryonic stem cells, specific cell-types, such as endothelial, epithelial, myocytes, adipose, luminal epithelial, basoepithelial, myoepithelial, stromal cells, etc.

Polynucleotides can be used in wide range of methods and compositions, including for detecting, diagnosing, staging, grading, assessing, prognosticating, etc. diseases and disorders associated with differentially-regulated genes of the present invention, for monitoring or assessing therapeutic and/or preventative measures, in ordered arrays, etc. Any method of detecting genes and polynucleotides of Tables 1 and 2 can be used; certainly, the present invention is not to be limited how such methods are implemented.

Along these lines, the present invention relates to methods of detecting differentially-regulated genes described herein in a sample comprising nucleic acid. Such methods can comprise one or more the following steps in any effective order, e.g., contacting said sample with a polynucleotide probe under conditions effective for said probe to hybridize specifically to nucleic acid in said sample, and detecting the presence or absence of probe hybridized to nucleic acid in said sample, wherein said probe is a polynucleotide which is Tables 1 and 2, a polynucleotide having, e.g., about 70%, 80%, 85%, 90%, 95%, 99%, or more sequence identity thereto, effective or specific fragments thereof, or complements thereto. The detection method can be applied to any sample, e.g., cultured primary, secondary, or established cell lines, tissue biopsy, blood, urine, stool, and other bodily fluids, for any purpose.

Contacting the sample with probe can be carried out by any effective means in any effective environment. It can be accomplished in a solid, liquid, frozen, gaseous, amorphous, solidified, coagulated, colloid, etc., mixtures thereof, matrix. For instance, a probe in an aqueous medium can be contacted with a sample which is also in an aqueous medium, or which is affixed to a solid matrix, or vice-versa.

Generally, as used throughout the specification, the term "effective conditions" means, e.g., the particular milieu in which the desired effect is achieved. Such a milieu, includes, e.g., appropriate buffers, oxidizing agents, reducing agents, pH, co-factors, temperature, ion concentrations, suitable age and/or stage of cell (such as, in particular part of the cell cycle, or at a particular stage where particular genes are being expressed) where cells are being used, culture conditions (including substrate, oxygen, carbon dioxide, etc.). When hybridization is the chosen means of achieving detection, the probe and sample can be combined such that the resulting conditions are functional for said probe to hybridize specifically to nucleic acid in said sample.

The phrase "hybridize specifically" indicates that the hybridization between single-stranded polynucleotides is based on nucleotide sequence complementarity. The effective conditions are selected such that the probe hybridizes to a preselected and/or definite target nucleic acid in the sample. For instance, if detection of a gene set forth in Tables 1 and 2 is desired, a probe can be selected which can hybridize to such target gene under high stringent conditions, without significant hybridization to other genes in the sample. To detect homologs of a gene set forth in Tables 1 and 2, the effective hybridization conditions can be less stringent, and/or the probe can comprise codon degeneracy, such that a homolog is detected in the sample.

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As already mentioned, the methods can be carried out by any effective process, e.g., by Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, *in situ* hybridization, etc., as indicated above. When PCR based techniques are used, two or more probes are generally used. One probe can be specific for a defined sequence which is characteristic of a selective polynucleotide, but the other probe can be specific for the selective polynucleotide, or specific for a more general sequence, e.g., a sequence such as polyA which is characteristic of mRNA, a sequence which is specific for a promoter, ribosome binding site, or other transcriptional features, a consensus sequence (e.g., representing a functional domain). For the former aspects, 5' and 3' probes (e.g., polyA, Kozak, etc.) are preferred which are capable of specifically hybridizing to the ends of transcripts. When PCR is utilized, the probes can also be referred to as "primers" in that they can prime a DNA polymerase reaction.

In addition to testing for the presence or absence of polynucleotides, the present invention also relates to determining the amounts at which polynucleotides of the present invention are expressed in sample and determining the differential expression of such polynucleotides in samples.. Such methods can involve substantially the same steps as described above for presence/absence detection, e.g., contacting with probe, hybridizing, and detecting hybridized probe, but using more quantitative methods and/or comparisons to standards.

The amount of hybridization between the probe and target can be determined by any suitable methods, e.g., PCR, RT-PCR, RACE PCR, Northern blot, polynucleotide microarrays, Rapid-Scan, etc., and includes both quantitative and qualitative measurements. For further details, see the hybridization methods described above and below. Determining by such hybridization whether the target is differentially expressed (e.g., up-regulated or

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differentially-regulated) in the sample can also be accomplished by any effective means. For instance, the target's expression pattern in the sample can be compared to its pattern in a known standard, such as in a normal tissue, or it can be compared to another gene in the same sample. When a second sample is utilized for the comparison, it can be a sample of normal tissue that is known not to contain diseased cells. The comparison can be performed on samples which contain the same amount of RNA (such as polyadenylated RNA or total RNA), or, on RNA extracted from the same amounts of starting tissue. Such a second sample can also be referred to as a control or standard. Hybridization can also be compared to a second target in the same tissue sample. Experiments can be performed that determine a ratio between the target nucleic acid and a second nucleic acid (a standard or control), e.g., in a normal tissue. When the ratio between the target and control are substantially the same in a normal and sample, the sample is determined or diagnosed not to contain cells. However, if the ratio is different between the normal and sample tissues, the sample is determined to contain cancer cells. The approaches can be combined, and one or more second samples, or second targets can be used. Any second target nucleic acid can be used as a comparison, including "housekeeping" genes, such as beta-actin, alcohol dehydrogenase, or any other gene whose expression does not vary depending upon the disease status of the cell.

Methods of identifying polymorphisms, mutations, etc., of a differentially-regulated gene

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Polynucleotides of the present invention can also be utilized to identify mutant alleles, SNPs, gene rearrangements and modifications, and other polymorphisms of the wild-type gene. Mutant alleles, polymorphisms, SNPs, etc., can be identified and isolated from cancers that are known, or suspected to have, a genetic component. Identification of such genes can be carried out routinely (see, above for more guidance), e.g., using PCR, hybridization techniques, direct sequencing, mismatch reactions (see, e.g., above), RFLP analysis, SSCP (e.g., Orita et al., *Proc. Natl. Acad. Sci.*, 86:2766, 1992), etc., where a polynucleotide having a sequence selected from Tables 1 and 2 is used as a probe, or genomic sequences thereof. The selected mutant alleles, SNPs, polymorphisms, etc., can be used diagnostically to determine whether a subject has, or is susceptible to a disorder associated with a differentially-regulated gene, as well as to design therapies and predict the outcome of the disorder. Methods involve, e.g., diagnosing a disorder associated with a differentially-regulated gene or determining susceptibility to a disorder, comprising, detecting the presence of a mutation in a gene selected from Tables 1 and 2. The detecting can be carried out by any

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effective method, e.g., obtaining cells from a subject, determining the gene sequence or structure of a target gene (using, e.g., mRNA, cDNA, genomic DNA, etc), comparing the sequence or structure of the target gene to the structure of the normal gene, whereby a difference in sequence or structure indicates a mutation in the gene in the subject.

Polynucleotides can also be used to test for mutations, SNPs, polymorphisms, etc., e.g., using mismatch DNA repair technology as described in U.S. Pat. No. 5,683,877; U.S. Pat. No. 5,656,430; Wu et al., *Proc. Natl. Acad. Sci.*, 89:8779-8783, 1992.

The present invention also relates to methods of detecting polymorphisms in a differentially-regulated gene, comprising, e.g., comparing the structure of: genomic DNA comprising all or part of said gene, mRNA comprising all or part of said gene, cDNA comprising all or part of said gene, or a polypeptide comprising all or part of said gene, with the structure of said gene as set forth herein. The methods can be carried out on a sample from any source, e.g., cells, tissues, body fluids, blood, urine, stool, hair, egg, sperm, etc.

These methods can be implemented in many different ways. For example, "comparing the structure" steps include, but are not limited to, comparing restriction maps, nucleotide sequences, amino acid sequences, RFLPs, DNAse sites, DNA methylation fingerprints (e.g., U.S. Pat. No. 6,214,556), protein cleavage sites, molecular weights, electrophoretic mobilities, charges, ion mobility, etc., between a standard gene and a test gene. The term "structure" can refer to any physical characteristics or configurations which can be used to distinguish between nucleic acids and polypeptides. The methods and instruments used to accomplish the comparing step depends upon the physical characteristics which are to be compared. Thus, various techniques are contemplated, including, e.g., sequencing machines (both amino acid and polynucleotide), electrophoresis, mass spectrometer (U.S. Pat. Nos. 6,093,541, 6,002,127), liquid chromatography, HPLC, etc.

To carry out such methods, "all or part" of the gene or polypeptide can be compared. For example, if nucleotide sequencing is utilized, the entire gene can be sequenced, including promoter, introns, and exons, or only parts of it can be sequenced and compared, e.g., exon 1, exon 2, etc.

#### Mutagenesis

Mutated polynucleotide sequences of the present invention are useful for various

purposes, e.g., to create mutations of the polypeptides they encode, to identify functional regions of genomic DNA, to produce probes for screening libraries, etc. Mutagenesis can be carried out routinely according to any effective method, e.g., oligonucleotide-directed (Smith, M., Ann. Rev. Genet. 19:423-463, 1985), degenerate oligonucleotide-directed (Hill et al., Method Enzymology, 155:558-568, 1987), region-specific (Myers et al., Science, 229:242-246, 1985; Derbyshire et al., Gene, 46:145, 1986; Ner et al., DNA, 7:127, 1988), linkerscanning (McKnight and Kingsbury, Science, 217:316-324, 1982), directed using PCR, recursive ensemble mutagenesis (Arkin and Yourvan, Proc. Natl. Acad. Sci., 89:7811-7815, 1992), random mutagenesis (e.g., U.S. Pat. Nos. 5,096,815; 5,198,346; and 5,223,409), sitedirected mutagenesis (e.g., Walder et al., Gene, 42:133, 1986; Bauer et al., Gene, 37:73, 1985; Craik, Bio Techniques, January 1985, 12-19; Smith et al., Genetic Engineering: Principles and Methods, Plenum Press, 1981), phage display (e.g., Lowman et al., Biochem. 30:10832-10837, 1991; Ladner et al., U.S. Pat. No. 5,223,409; Huse, WIPO Publication WO 92/06204), etc. Desired sequences can also be produced by the assembly of target sequences using mutually priming oligonucleotides (Uhlmann, Gene, 71:29-40, 1988). For directed mutagenesis methods, analysis of the three-dimensional structure of a polypeptide can be used to guide and facilitate making mutants which effect polypeptide activity. Sites of substrate-enzyme interaction or other biological activities can also be determined by analysis of crystal structure as determined by such techniques as nuclear magnetic resonance, crystallography or photoaffinity labeling. See, for example, de Vos et al., Science 255:306-312, 1992; Smith et al., J. Mol. Biol. 224:899-904, 1992; Wlodaver et al., FEBS Lett. 309:59-64, 1992.

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In addition, libraries of differentially-regulated genes and fragments thereof can be used for screening and selection of gene variants. For instance, a library of coding sequences can be generated by treating a double-stranded DNA with a nuclease under conditions where the nicking occurs, e.g., only once per molecule, denaturing the double-stranded DNA, renaturing it to for double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single-stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting DNAs into an expression vectore. By this method, expression libraries can be made comprising "mutagenized" differentially-regulated genes. The entire coding sequence or parts thereof can be used.

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Polynucleotide expression, polypeptides produced thereby, and specific-binding partners thereto.

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A polynucleotide according to the present invention can be expressed in a variety of different systems, in vitro and in vivo, according to the desired purpose. For example, a polynucleotide can be inserted into an expression vector, introduced into a desired host, and cultured under conditions effective to achieve expression of a polypeptide coded for by the polynucleotide, to search for specific binding partners. Effective conditions include any culture conditions which are suitable for achieving production of the polypeptide by the host cell, including effective temperatures, pH, medium, additives to the media in which the host cell is cultured (e.g., additives which amplify or induce expression such as butyrate, or methotrexate if the coding polynucleotide is adjacent to a dhfr gene), cycloheximide, cell densities, culture dishes, etc. A polynucleotide can be introduced into the cell by any effective method including, e.g., naked DNA, calcium phosphate precipitation, electroporation, injection, DEAE-Dextran mediated transfection, fusion with liposomes, association with agents which enhance its uptake into cells, viral transfection. A cell into which a polynucleotide of the present invention has been introduced is a transformed host cell. The polynucleotide can be extrachromosomal or integrated into a chromosome(s) of the host cell. It can be stable or transient. An expression vector is selected for its compatibility with the host cell. Host cells include, mammalian cells, e.g., COS, CV1, BHK, CHO, HeLa, LTK, NIH 3T3, PC-3 (CRL-1435), LNCaP (CRL-1740), CA-HPV-10 (CRL-2220), PZ-HPV-7 (CRL-2221), MDA-PCa 2b (CRL-2422), 22Rv1 (CRL2505), NCI-H660 (CRL-5813), HS 804.Sk (CRL-7535), LNCaP-FGF (CRL-10995), RWPE-1 (CRL-11609), RWPE-2 (CRL-11610), PWR-1E (CRL 11611), rat MAT-Ly-LuB-2 (CRL-2376), and other prostate cells, insect cells, such as Sf9 (S. frugipeda) and Drosophila, bacteria, such as E. coli, Streptococcus, bacillus, yeast, such as Sacharomyces, S. cerevisiae, fungal cells, plant cells, embryonic or adult stem cells (e.g., mammalian, such as mouse or human).

Expression control sequences are similarly selected for host compatibility and a desired purpose, e.g., high copy number, high amounts, induction, amplification, controlled expression. Other sequences which can be employed include enhancers such as from SV40, CMV, RSV, inducible promoters, cell-type specific elements, or sequences which allow selective or specific cell expression. Promoters that can be used to drive its expression, include, e.g., the endogenous promoter, MMTV, SV40, trp, lac, tac, or T7 promoters for bacterial hosts; or alpha factor, alcohol oxidase, or PGH promoters for yeast. RNA

promoters can be used to produced RNA transcripts, such as T7 or SP6. See, e.g., Melton et al., *Polynucleotide Res.*, 12(18):7035-7056, 1984; Dunn and Studier. *J. Mol. Bio.*, 166:477-435, 1984; U.S. Pat. No. 5,891,636; Studier et al., *Gene Expression Technology, Methods in Enzymology*, 85:60-89, 1987. In addition, as discussed above, translational signals (including in-frame insertions) can be included.

When a polynucleotide is expressed as a heterologous gene in a transfected cell line, the gene is introduced into a cell as described above, under effective conditions in which the gene is expressed. The term "heterologous" means that the gene has been introduced into the cell line by the "hand-of-man." Introduction of a gene into a cell line is discussed above. The transfected (or transformed) cell expressing the gene can be lysed or the cell line can be used intact.

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For expression and other purposes, a polynucleotide can contain codons found in a naturally-occurring gene, transcript, or cDNA, for example, e.g., as set forth in Tables 1 and 2, or it can contain degenerate codons coding for the same amino acid sequences. For instance, it may be desirable to change the codons in the sequence to optimize the sequence for expression in a desired host. See, e.g., U.S. Pat. Nos. 5,567,600 and 5,567,862.

A polypeptide according to the present invention can be recovered from natural sources, transformed host cells (culture medium or cells) according to the usual methods, including, detergent extraction (e.g., non-ionic detergent, Triton X-100, CHAPS, octylglucoside, Igepal CA-630), ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxyapatite chromatography, lectin chromatography, gel electrophoresis. Protein refolding steps can be used, as necessary, in completing the configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for purification steps. Another approach is express the polypeptide recombinantly with an affinity tag (Flag epitope, HA epitope, myc epitope, 6xHis, maltose binding protein, chitinase, etc) and then purify by anti-tag antibody-conjugated affinity chromatography.

The present invention also relates to antibodies, and other specific-binding partners, which are specific for polypeptides encoded by polynucleotides of the present invention.

Antibodies, e.g., polyclonal, monoclonal, recombinant, chimeric, humanized, single-chain, Fab, and fragments thereof, can be prepared according to any desired method. See, also, screening recombinant immunoglobulin libraries (e.g., Orlandi et al., *Proc. Natl. Acad. Sci.*,

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86:3833-3837, 1989; Huse et al., *Science*, 256:1275-1281, 1989); in vitro stimulation of lymphocyte populations; Winter and Milstein, *Nature*, 349: 293-299, 1991. The antibodies can be IgM, IgG, subtypes, IgG2a, IgG1, etc. Antibodies, and immune responses, can also be generated by administering naked DNA See, e.g., U.S. Pat. Nos. 5,703,055; 5,589,466; 5,580,859. Antibodies can be used from any source, including, goat, rabbit, mouse, chicken (e.g., IgY; see, Duan, W0/029444 for methods of making antibodies in avian hosts, and harvesting the antibodies from the eggs). An antibody specific for a polypeptide means that the antibody recognizes a defined sequence of amino acids within or including the polypeptide. Other specific binding partners include, e.g., aptamers and PNA, can be prepared against specific epitopes or domains of differentially regulated genes.

The preparation of polyclonal antibodies is well-known to those skilled in the art. See, for example, Green et al., Production of Polyclonal Antisera, in IMMUNOCHEMICAL PROTOCOLS (Manson, ed.), pages 1-5 (Humana Press 1992); Coligan et al., Production of Polyclonal Antisera in Rabbits, Rats, Mice and Hamsters, in CURRENT PROTOCOLS IN IMMUNOLOGY, section 2.4.1 (1992). The preparation of monoclonal antibodies likewise is conventional. See, for example, Kohler & Milstein, Nature 256:495 (1975); Coligan et al., sections 2.5.1-2.6.7; and Harlow et al., ANTIBODIES: A LABORATORY MANUAL, page 726 (Cold Spring Harbor Pub. 1988).

Antibodies can also be humanized, e.g., where they are to be used therapeutically. Humanized monoclonal antibodies are produced by transferring mouse complementarity determining regions from heavy and light variable chains of the mouse immunoglobulin into a human variable domain, and then substituting human residues in the framework regions of the murine counterparts. The use of antibody components derived from humanized monoclonal antibodies obviates potential problems associated with the immunogenicity of murine constant regions. General techniques for cloning murine immunoglobulin variable domains are described, for example, by Orlandi et al., Proc. Nat 'l Acad. Sci. USA 86:3833 (1989), which is hereby incorporated in its entirety by reference. Techniques for producing humanized monoclonal antibodies are described, for example, in U.S. Pat. No. 6,054,297, Jones et al., Nature 321: 522 (1986); Riechmann et al., Nature 332: 323 (1988); Verhoeyen et al., Science 239: 1534 (1988); Carter et al., Proc. Nat'l Acad. Sci. USA 89: 4285 (1992); Sandhu, Crit. Rev. Biotech. 12: 437 (1992); and Singer et al., J. Immunol. 150: 2844 (1993).

Antibodies of the invention also may be derived from human antibody fragments isolated from a combinatorial immunoglobulin library. See, for example, Barbas et al.,

METHODS: A COMPANION TO METHODS IN ENZYMOLOGY, VOL. 2, page 119 (1991); Winter et al., Ann. Rev. Immunol. 12: 433 (1994). Cloning and expression vectors that are useful for producing a human immunoglobulin phage library can be obtained commercially, for example, from STRATAGENE Cloning Systems (La Jolla, Calif.).

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In addition, antibodies of the present invention may be derived from a human monoclonal antibody. Such antibodies are obtained from transgenic mice that have been "engineered" to produce specific human antibodies in response to antigenic challenge. In this technique, elements of the human heavy and light chain loci are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy and light chain loci. The transgenic mice can synthesize human antibodies specific for human antigens and can be used to produce human antibody-secreting hybridomas. Methods for obtaining human antibodies from transgenic mice are described, e.g., in Green et al., Nature Genet. 7:13 (1994); Lonberg et al., Nature 368:856 (1994); and Taylor et al., Int. Immunol. 6:579 (1994).

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Antibody fragments of the present invention can be prepared by proteolytic hydrolysis of the antibody or by expression in E. coli of nucleic acid encoding the fragment. Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies by conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S fragment denoted F(ab').sub.2. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulfhydryl groups resulting from cleavage of disulfide linkages, to produce 3.5S Fab' monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two monovalent Fab' fragments and an Fc fragment directly. These methods are described, for example, by Goldenberg, U.S. Pat. No. 4,036,945 and No. 4,331,647, and references contained therein. These patents are hereby incorporated in their entireties by reference. See also Nisoiihoff et al., Arch. Biochem. Biophys. 89:230 (1960); Porter, Biochem. J. 73:119 (1959); Edelman et al., METHODS IN ENZYMOLOGY, VOL. 1, page 422 (Academic Press 1967); and Coligan et al. at sections 2.8.1-2.8.10 and 2.10.1-2.10.4.

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Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical, or genetic techniques can also be used. For example, Fv fragments comprise an association of V.sub.H and V.sub.L chains. This association may be noncovalent, as described in Inbar et al., Proc. Nat'l Acad. Sci. USA 69:2659 (1972). Alternatively, the

variable chains can be linked by an intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde. See, e.g., Sandhu, supra. Preferably, the Fv fragments comprise V.sub.H and V.sub.L chains connected by a peptide linker. These single-chain antigen binding proteins (sFv) are prepared by constructing a structural gene comprising nucleic acid sequences encoding the V.sub.H and V.sub.L domains connected by an oligonucleotide. The structural gene is inserted into an expression vector, which is subsequently introduced into a host cell such as E. coli. The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Methods for producing sFvs are described, for example, by Whitlow et al., METHODS: A COMPANION TO METHODS IN ENZYMOLOGY, VOL. 2, page 97 (1991); Bird etal., Science 242:423-426 (1988); Ladneret al., U.S. Pat. No. 4,946,778; Pack et al., Bio/Technology 11: 1271-77 (1993); and Sandhu, supra.

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Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells. See, for example, Larrick et al., METHODS: A COMPANION TO METHODS IN ENZYMOLOGY, VOL. 2, page 106 (1991).

The term "antibody" as used herein includes intact molecules as well as fragments thereof, such as Fab, F(ab')2, and Fv which are capable of binding to an epitopic determinant present in Bin1 polypeptide. Such antibody fragments retain some ability to selectively bind with its antigen or receptor. The term "epitope" refers to an antigenic determinant on an antigen to which the paratope of an antibody binds. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Antibodies can be prepared against specific epitopes or polypeptide domains.

Antibodies which bind to a differentially-regulated polypeptide of the present invention can be prepared using an intact polypeptide or fragments containing small peptides of interest as the immunizing antigen. For example, it may be desirable to produce antibodies that specifically bind to the N- or C-terminal domains of said polypeptide. The polypeptide or peptide used to immunize an animal which is derived from translated cDNA or chemically synthesized which can be conjugated to a carrier protein, if desired. Such commonly used

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carriers which are chemically coupled to the immunizing peptide include keyhole limpet hemocyanin (KLH), thyroglobulin, bovine serum albumin (BSA), and tetanus toxoid.

Polyclonal or monoclonal antibodies can be further purified, for example, by binding to and elution from a matrix to which the polypeptide or a peptide to which the antibodies were raised is bound. Those of skill in the art will know of various techniques common in the immunology arts for purification and/or concentration of polyclonal antibodies, as well as monoclonal antibodies (See for example, Coligan, et al., Unit 9, *Current Protocols in Immunology*, Wiley Interscience, 1994, incorporated by reference).

Anti-idiotype technology can also be used to produce invention monoclonal antibodies which mimic an epitope. For example, an anti-idiotypic monoclonal antibody made to a first monoclonal antibody will have a binding domain in the hypervariable region which is the "image" of the epitope bound by the first monoclonal antibody.

## Methods of detecting polypeptides

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Polypeptides coded for by a differentially-regulated gene of the present invention can be detected, visualized, determined, quantitated, etc. according to any effective method. useful methods include, e.g., but are not limited to, immunoassays, RIA (radioimmunassay), ELISA, (enzyme-linked-immunosorbent assay), immunoflourescence, flow cytometry, histology, electron microscopy, light microscopy, in situ assays, immunoprecipitation, Western blot, etc.

Immunoassays may be carried in liquid or on biological support. For instance, a sample (e.g., blood, stool, urine, cells, tissue, body fluids, etc.) can be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support that is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled differentially-regulated gene specific antibody. The solid phase support can then be washed with a buffer a second time to remove unbound antibody. The amount of bound label on solid support may then be detected by conventional means.

A "solid phase support or carrier" includes any support capable of binding an antigen, antibody, or other specific binding partner. Supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, and magnetite. A support material can have any structural or physical configuration. Thus, the support configuration may be spherical, as in a bead, or cylindrical,

as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads

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One of the many ways in which gene peptide-specific antibody can be detectably labeled is by linking it to an enzyme and using it in an enzyme immunoassay (EIA). See, e.g., Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)," 1978, Diagnostic Horizons 2, 1-7, Microbiological Associates Quarterly Publication, Walkersville, Md.); Voller, A. et al., 1978, J. Clin. Pathol. 31, 507-520; Butler, J. E., 1981, Meth. Enzymol. 73, 482-523; Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, Fla.. The enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety that can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes that can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, .alpha.-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, .beta.galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods that employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect differentially-regulated peptides through the use of a radioimmunoassay (RIA). See, e.g., Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986. The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography.

It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycocrythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine. The antibody can also be detectably

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labeled using fluorescence emitting metals such as those in the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

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#### Tissue and Disease

The prostate is a secretory organ surrounding the neck of the bladder and urethra. Its primary function is to produce fluids and other materials necessary for sperm transport and maintenance. Structurally, it has both glandular and nonglandular components. The glandular component is predominantly comprised of ducts and acini responsible for the production and transport prostatic fluids. Epithelial cells are the main identifiable cell found in these regions, primarily of the basal and secretory types, but also endocrine-paracrine and transitional epithelial. The non-glandular component contains the capsular and muscle tissues, which, respectively, hold the organ together and function in fluid discharge. See, e.g., Histology for Pathologists, Sternberg, S.S., editor, Raven Press, NY, 1992, Chapter 40.

The major diseases of the prostate include, e.g., prostatic hyperplasia (BPH), prostatitis, and prostate cancer (e.g., prostatic adenocarcinoma). BPH is a benign, proliferative disease of the prostatic epithelial cells. While it may cause urinary tract obstruction in some patients, for the most part, it is generally asymptomatic. Prostate cancer, on the other hand, is the most common form of cancer in white males in the United States, occurring predominantly in males over age 50. The prevalence of prostate diseases, such as prostate cancer, has made the discovery of prostate selective markers and gene expression patterns of great importance.

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The most common scale of assessing prostate pathology is the Gleason grading system. See, e.g., Bostwick, *Am. J. Clin. Path.*, 102: s38-s56, 1994. Once the cancer is identified, staging can assess the size, location, and extent of the cancer. Several different staging scales are commonly used, including stages A-D, and Tumor-Nodes-Metastases (TNM). For treatment, diagnosis, staging, etc., of prostate conditions, methods can be carried out analogously to, and in combination with, U.S. Pat. Nos. 6,107,090; 6,057,116; 6,034,218; 6,004,267; 5,919,638; 5,882,864; 5,763,202; 5,747,264; 5,688,649; 5,552,277.

In addition, the present invention relates to methods of assessing a therapeutic or preventative intervention in a subject having a prostate cancer, comprising, e.g., detecting the expression levels of differentially-regulated target genes, wherein the target genes comprise a gene which is represented by a sequence selected from Tables 1 and 2, or, a gene represented by a sequence having 95% sequence identity or more to a sequence selected from Tables 1 and 2. By "therapeutic or preventative intervention," it is meant, e.g., a drug administered a patient, surgery, radiation, chemotherapy, and other measures taken to prevent a cancer or treat a cancer.

Grading, staging, comparing, assessing, methods and compositions

The present invention also relates to methods and compositions for staging and grading cancers. As already defined, staging relates to determining the extent of a cancer's spread, including its size and the degree to which other tissues, such as lymph nodes are involved in the cancer. Grading refers to the degree of a cell's retention of the characteristics of the tissue of its origin. A lower grade cancer comprises tumor cells that more closely resemble normal cells than a medium or higher grade cancer. Grading can be a useful diagnostic and prognostic tool. Higher grade cancers usually behave more aggressively than lower grade cancers. Thus, knowledge of the cancer grade, as well as its stage, can be a significant factor in the choice of the appropriate therapeutic intervention for the particular patient, e.g., surgery, radiation, chemotherapy, etc. Staging and grading can also be used in conjunction with a therapy to assess its efficacy, to determine prognosis, to determine effective dosages, etc.

Various methods of staging and grading cancers can be employed in accordance with the present invention. A "cell expression profile" or "cell expression fingerprint" is a representation of the expression of various different genes (e.g., polynucleotide sequences of SEQ ID NOS 1-107) in a given cell or sample comprising cells. These cell expression

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profiles can be useful as reference standards. The cell expression fingerprints can be used alone for grading, or in combination with other grading methods.

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The present invention also relates to methods and compositions for diagnosing a prostate cancer, or determining susceptibility to a prostate cancer, using polynucleotides, polypeptides, and specific-binding partners of the present invention to detect, assess, determine, etc., differentially-regulated genes of the present invention. In such methods, the gene can serve as a marker for prostate cancer, e.g., where the gene, when mutant, is a direct cause of the prostate cancer; where the gene is affected by another gene(s) which is directly responsible for the prostate cancer, e.g., when the gene is part of the same signaling pathway as the directly responsible gene; and, where the gene is chromosomally linked to the gene(s) directly responsible for the prostate cancer, and segregates with it. Many other situations are possible. To detect, assess, determine, etc., a probe specific for the gene can be employed as described above and below. Any method of detecting and/or assessing the gene can be used, including detecting expression of the gene using polynucleotides, antibodies, or other specific-binding partners.

The present invention relates to methods of diagnosing a disorder associated with prostate cancer, or determining a subject's susceptibility to such prostate cancer, comprising, e.g., assessing the expression of a differentially-regulated gene in a tissue sample comprising tissue or cells suspected of having prostate cancer (e.g., where the sample comprises prostate). The phrase "diagnosing" indicates that it is determined whether the sample has a prostate cancer cells. "Determining a subject's susceptibility to a prostate cancer" indicates that the subject is assessed for whether s/he is predisposed to get such a disease or disorder, where the predisposition is indicated by abnormal expression of the gene (e.g., gene mutation, gene expression pattern is not normal, etc.). Predisposition or susceptibility to a disease may result when a such disease is influenced by epigenetic, environmental, etc., factors.

By the phrase "assessing expression of a differentially-regulated gene," it is meant that the functional status of the gene is evaluated. This includes, but is not limited to, measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene. Thus, the term "assessing expression" includes evaluating the all aspects of the transcriptional and translational machinery of the gene. For instance, if a promoter defect causes, or is suspected of

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causing, the disorder, then a sample can be evaluated (i.e., "assessed") by looking (e.g., sequencing or restriction mapping) at the promoter sequence in the gene, by detecting transcription products (e.g., RNA), by detecting translation product (e.g., polypeptide). Any measure of whether the gene is functional can be used, including, polypeptide, polynucleotide, and functional assays for the gene's biological activity.

In making the assessment, it can be useful to compare the results to a normal gene, e.g., a gene which is not associated with the disorder. The nature of the comparison can be determined routinely, depending upon how the assessing is accomplished. If, for example, the mRNA levels of a sample is detected, then the mRNA levels of a normal can serve as a comparison, or a gene which is known not to be affected by the disorder. Methods of detecting mRNA are well known, and discussed above, e.g., but not limited to, Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, etc. Similarly, if polypeptide production is used to evaluate the gene, then the polypeptide in a normal tissue sample can be used as a comparison, or, polypeptide from a different gene whose expression is known not to be affected by the disorder. These are only examples of how such a method could be carried out.

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Assessing the effects of therapeutic and preventative interventions (e.g., administration of a drug, chemotherapy, radiation, etc.) on prostate cancer is a major effort in drug discovery, clinical medicine, and pharmacogenomics. The evaluation of therapeutic and preventative measures, whether experimental or already in clinical use, has broad applicability, e.g., in clinical trials, for monitoring the status of a patient, for analyzing and assessing animal models, and in any scenario involving cancer treatment and prevention. Analyzing the expression profiles of polynucleotides of the present invention can be utilized as a parameter by which interventions are judged and measured. Treatment of a disorder can change the expression profile in some manner which is prognostic or indicative of the drug's effect on it. Changes in the profile can indicate, e.g., drug toxicity, return to a normal level, etc. Accordingly, the present invention also relates to methods of monitoring or assessing a therapeutic or preventative measure (e.g., chemotherapy, radiation, anti-neoplastic drugs, antibodies, etc.) in a subject having prostate cancer, or, susceptible to such a disorder, comprising, e.g., detecting the expression levels of one or more differentially-regulated genes of the present invention. A subject can be a cell-based assay system, non-human animal model, human patient, etc. Detecting can be accomplished as described for the methods above and below. By

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"therapeutic or preventative intervention," it is meant, e.g., a drug administered to a patient, surgery, radiation, chemotherapy, and other measures taken to prevent, treat, or diagnose prostate cancer.

Expression can be assessed in any sample comprising any tissue or cell type, body fluid, etc., as discussed for other methods of the present invention, including cells from prostate can be used, or cells derived from prostate. By the phrase "cells derived from prostate," it is meant that the derived cells originate from prostate, e.g., when metastasis from a primary tumor site has occurred, when a progenitor-type or pluripotent cell gives rise to other cells, etc.

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## Identifying agent methods

The present invention also relates to methods of identifying agents, and the agents themselves, which modulate prostate cancer genes. These agents can be used to modulate the biological activity of the polypeptide encoded for the gene, or the gene, itself. Agents which regulate the gene or its product are useful in variety of different environments, including as medicinal agents to treat or prevent disorders associated with prostate cancer genes and as research reagents to modify the function of tissues and cell.

Methods of identifying agents generally comprise steps in which an agent is placed in contact with the gene, transcription product, translation product, or other target, and then a determination is performed to assess whether the agent "modulates" the target. The specific method utilized will depend upon a number of factors, including, e.g., the target (i.e., is it the gene or polypeptide encoded by it), the environment (e.g., in vitro or in vivo), the composition of the agent, etc.

For modulating the expression of a prostate cancer gene, a method can comprise, in any effective order, one or more of the following steps, e.g., contacting a prostate cancer gene (e.g., in a cell population) with a test agent under conditions effective for said test agent to modulate the expression of the prostate cancer, and determining whether said test agent modulates said gene. An agent can modulate expression of a gene at any level, including transcription, translation, and/or perdurance of the nucleic acid (e.g., degradation, stability, etc.) in the cell. For modulating the biological activity of prostate cancer polypeptides, a method can comprise, in any effective order, one or more of the following steps, e.g., contacting a polypeptide (e.g., in a cell, lysate, or isolated) with a test agent under conditions

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effective for said test agent to modulate the biological activity of said polypeptide, and determining whether said test agent modulates said biological activity.

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Contacting a gene or polypeptidewith the test agent can be accomplished by any suitable method and/or means that places the agent in a position to functionally control its expression or biological activity. Functional control indicates that the agent can exert its physiological effect on the gene or polypeptide through whatever mechanism it works. The choice of the method and/or means can depend upon the nature of the agent and the condition and type of environment in which the gene or polypeptide is presented, e.g., lysate, isolated, or in a cell population (such as, *in vivo*, *in vitro*, organ explants, etc.). For instance, if the cell population is an *in vitro* cell culture, the agent can be contacted with the cells by adding it directly into the culture medium. If the agent cannot dissolve readily in an aqueous medium, it can be incorporated into liposomes, or another lipophilic carrier, and then administered to the cell culture. Contact can also be facilitated by incorporation of agent with carriers and delivery molecules and complexes, by injection, by infusion, etc.

After the agent has been administered in such a way that it can gain access to the gene or polypeptide, it can be determined whether the test agent modulates the gene or polypeptide expression or biological activity. Modulation can be of any type, quality, or quantity, e.g., increase, facilitate, enhance, up-regulate, stimulate, activate, amplify, augment, induce, decrease, down-regulate, diminish, lessen, reduce, etc. The modulatory quantity can also encompass any value, e.g., 1%, 5%, 10%, 50%, 75%, 1-fold, 2-fold, 5-fold, 10-fold, 100-fold, etc. To modulate gene expression means, e.g., that the test agent has an effect on its expression, e.g., to effect the amount of transcription, to effect RNA splicing, to effect translation of the RNA into polypeptide, to effect RNA or polypeptide stability, to effect polyadenylation or other processing of the RNA, to effect post-transcriptional or post-translational processing, etc. To modulate biological activity means, e.g., that a functional activity of the polypeptide is changed in comparison to its normal activity in the absence of the agent. This effect includes, increase, decrease, block, inhibit, enhance, etc.

A test agent can be of any molecular composition, e.g., chemical compounds, biomolecules, such as polypeptides, lipids, nucleic acids (e.g., antisense to a polynucleotide sequence selected from Tables 1 and 2, or genomic sequences thereof), carbohydrates, antibodies, ribozymes, double-stranded RNA, aptamers, etc. For example, if a polypeptide to be modulated is a cell-surface molecule, a test agent can be an antibody that specifically recognizes it and, e.g., causes the polypeptide to be internalized, leading to its down

regulation on the surface of the cell. Such an effect does not have to be permanent, but can require the presence of the antibody to continue the down-regulatory effect. Antibodies can also be used to modulate the biological activity a polypeptide in a lysate or other cell-free form. Antisense can also be used as test agents to modulate gene expression.

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### Markers

The polynucleotides of the present invention can be used with other markers, especially prostate and prostate cancer markers to identity, detect, stage, diagnosis, determine, prognosticate, treat, etc., tissue, diseases and conditions, etc, of the prostate.

Markers can be polynucleotides, polypeptides, antibodies, ligands, specific binding partners, etc.

A number of genes and gene products have been identified which are associated with prostate cancer metastasis and/or progression, e.g., PSA, KAII (shows decreased expression in metastatic cells; Dong et al., *Science*, 268:884-6, 1995), D44 isoforms (differentially-regulated during carcinoma progression; Noordzij et al., *Clin. Cancer Res.*, 3:805-15, 1997), p53 (Effert et al., *J. Urol.*, 150:257-61, 1993), Rb, CDKN2, E-cadherin, PTEN (Hamilton et al., *Br. J. Cancer*, 82:1671-6, 2000; Dong et al., *Clin. Cancer Res.*, 7:304-308, 2001), bcl-2, prostatic acid phosphatase (PAP), prostate specific membrane antigen (e.g., U.S. Pat. Nos. 5,538,866 and 6,107,090), Smad3 (e.g., Kang et al., *Proc. Natl. Acad. Sci.*, 98:3018-3023, 2001), TGF-beta, and other oncogenes and tumor suppressor genes. See, also, Myers and Grizzle, *Eur. Urol.*, 30:153-166, 1996, for other biomarkers associated with prostatic carcinoma, such as PCNA, p185-erbB-2, p180erbB-3, TAG-72, nm23-H1 and FASE. Such markers can be used in combination with the methods of the present invention to facilitate identifying, grading, staging, prognostication, etc, of conditions and diseases of the prostate.

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#### Therapeutics

Selective polynucleotides, polypeptides, and specific-binding partners thereto, can be utilized in therapeutic applications, especially to treat prostate cancer. Useful methods include, but are not limited to, immunotherapy (e.g., using specific-binding partners to polypeptides), vaccination (e.g., using a selective polypeptide or a naked DNA encoding such polypeptide), protein or polypeptide replacement therapy, gene therapy (e.g., germ-line correction, antisense), etc.

Various immunotherapeutic approaches can be used. For instance, unlabeled

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antibody that specifically recognizes a tissue-specific antigen can be used to stimulate the body to destroy or attack the cancer, to cause down-regulation, to produce complement-mediated lysis, to inhibit cell growth, etc., of target cells which display the antigen, e.g., analogously to how c-erbB-2 antibodies are used to treat breast cancer. In addition, antibody can be labeled or conjugated to enhance its deleterious effect, e.g., with radionuclides and other energy emitting entitities, toxins, such as ricin, exotoxin A (ETA), and diphtheria, cytotoxic or cytostatic agents, immunomodulators, chemotherapeutic agents, etc. See, e.g., U.S. Pat. No. 6,107,090.

An antibody or other specific-binding partner can be conjugated to a second molecule, such as a cytotoxic agent, and used for targeting the second molecule to a tissue-antigen positive cell (Vitetta, E. S. et al., 1993, Immunotoxin therapy, in DeVita, Jr., V. T. et al., eds, Cancer: Principles and Practice of Oncology, 4th ed., J. B. Lippincott Co., Philadelphia, 2624-2636). Examples of cytotoxic agents include, but are not limited to, antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, radioisotopes and chemotherapeutic agents. Further examples of cytotoxic agents include, but are not limited to ricin, doxorubicin, daunorubicin, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin D, 1-dehydrotestosterone, diptheria toxin, Pseudomonas exotoxin (PE) A, PE40, abrin, elongation factor-2 and glucocorticoid. Techniques for conjugating therapeutic agents to antibodies are well.

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In addition to immunotherapy, polynucleotides and polypeptides can be used as targets for non-immunotherapeutic applications, e.g., using compounds which interfere with function, expression (e.g., antisense as a therapeutic agent), assembly, etc. RNA interference can be used in vivtro and in vivo to silence differentially-expressed genes when its expression contributes to a disease (but also for other purposes, e.g., to identify the gene's function to change a developmental pathway of a cell, etc.). See, e.g., Sharp and Zamore, *Science*, 287:2431-2433, 2001; Grishok et al., *Science*, 287:2494, 2001.

Delivery of therapeutic agents can be achieved according to any effective method, including, liposomes, viruses, plasmid vectors, bacterial delivery systems, orally, systemically, etc. Therapeutic agents of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intraperitoneal, topical, transdermal (e.g., using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosal, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-

arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

In addition to therapeutics, *per se*, the present invention also relates to methods of treating prostate cancer showing altered expression of differentially-regulated genes, such as Tables 1 and 2, comprising, e.g., administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of said genes and/or which is effective in treating said disease. The term "treating" is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, etc., of a disease or disorder. By the phrase "altered expression," it is meant that the disease is associated with a mutation in the gene, or any modification to the gene (or corresponding product) which affects its normal function. Thus, expression of a differentially-regulated gene refers to, e.g., transcription, translation, splicing, stability of the mRNA or protein product, activity of the gene product, differential expression, etc.

Any agent which "treats" the disease can be used. Such an agent can be one which regulates the expression of the gene. Expression refers to the same acts already mentioned, e.g. transcription, translation, splicing, stability of the mRNA or protein product, activity of the gene product, differential expression, etc. For instance, if the condition was a result of a complete deficiency of the gene product, administration of gene product to a patient would be said to treat the disease and regulate the gene's expression. Many other possible situations are possible, e.g., where the gene is aberrantly expressed, and the therapeutic agent regulates the aberrant expression by restoring its normal expression pattern.

### 25 Antisense

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Antisense polynucleotide (e.g., RNA) can also be prepared from a polynucleotide according to the present invention, preferably an anti-sense to a gene of Tables 1 and 2. Antisense polynucleotide can be used in various ways, such as to regulate or modulate expression of the polypeptides they encode, e.g., inhibit their expression, for in situ hybridization, for therapeutic purposes, for making targeted mutations (in vivo, triplex, etc.) etc. For guidance on administering and designing anti-sense, see, e.g., U.S. Pat. Nos. 6,200,960, 6,200,807, 6,197,584, 6,190,869, 6,190,661, 6,187,587, 6,168,950, 6,153,595, 6,150,162, 6,133,246, 6,117,847, 6,096,722, 6,087,343, 6,040,296, 6,005,095, 5,998,383,

5,994,230, 5,891,725, 5,885,970, and 5,840,708. An antisense polynucleotides can be operably linked to an expression control sequence. A total length of about 35 bp can be used in cell culture with cationic liposomes to facilitate cellular uptake, but for *in vivo* use, preferably shorter oligonucleotides are administered, e.g. 25 nucleotides.

Antisense polynucleotides can comprise modified, nonnaturally-occurring nucleotides and linkages between the nucleotides (e.g., modification of the phosphate-sugar backbone; methyl phosphonate, phosphorothioate, or phosphorodithioate linkages; and 2'-O-methyl ribose sugar units), e.g., to enhance in vivo or in vitro stability, to confer nuclease resistance, to modulate uptake, to modulate cellular distribution and compartmentalization, etc. Any effective nucleotide or modification can be used, including those already mentioned, as known in the art, etc., e.g., disclosed in U.S. Pat. Nos. 6,133,438; 6,127,533; 6,124,445; 6,121,437; 5,218,103 (e.g., nucleoside thiophosphoramidites); 4,973,679; Sproat et al., "2'-O-Methyloligoribonucleotides: synthesis and applications," Oligonucleotides and Analogs A Practical Approach, Eckstein (ed.), IRL Press, Oxford, 1991, 49-86; Iribarren et al., "2'O-Alkyl Oligoribonucleotides as Antisense Probes," Proc. Natl. Acad. Sci. USA, 1990, 87, 7747-7751; Cotton et al., "2'-O-methyl, 2'-O-ethyl oligoribonucleotides and phosphorothioate oligodeoxyribonucleotides as inhibitors of the in vitro U7 snRNP-dependent mRNA processing event," Nucl. Acids Res., 1991, 19, 2629-2635.

# 20 Arrays

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The present invention also relates to an ordered array of polynucleotide probes and specific-binding partners (e.g., antibodies) for detecting the expression of differentially-regulated genes in a sample, comprising, one or more polynucleotide probes or specific binding partners associated with a solid support, wherein each probe is specific for said genes, and the probes comprise a nucleotide sequence of Tables 1 and 2 which is specific for said gene, a nucleotide sequence having sequence identity to Tables 1 and 2 which is specific for said gene or polynucleotide, or complements thereto, or a specific-binding partner which is specific for said genes.

The phrase "ordered array" indicates that the probes are arranged in an identifiable or position-addressable pattern, e.g., such as the arrays disclosed in U.S. Pat. Nos. 6,156,501, 6,077,673, 6,054,270, 5,723,320, 5,700,637, WO09919711, WO00023803. The probes are associated with the solid support in any effective way. For instance, the probes can be bound to the solid support, either by polymerizing the probes on the substrate, or by attaching a

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probe to the substrate. Association can be, covalent, electrostatic, noncovalent, hydrophobic, hydrophilic, noncovalent, coordination, adsorbed, absorbed, polar, etc. When fibers or hollow filaments are utilized for the array, the probes can fill the hollow orifice, be absorbed into the solid filament, be attached to the surface of the orifice, etc. Probes can be of any effective size, sequence identity, composition, etc., as already discussed.

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Ordered arrays can further comprise polynucleotide probes or specific-binding partners which are specific for other genes, including genes specific for prostate or disorders associated with prostate, such as prostate cancer.

### 10 Transgenic animals

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The present invention also relates to transgenic animals comprising differentially-regulated genes of the present invention. Such genes, as discussed in more detail below, include, but are not limited to, functionally-disrupted genes, mutated genes, ectopically or selectively-expressed genes, inducible or regulatable genes, etc. These transgenic animals can be produced according to any suitable technique or method, including homologous recombination, mutagenesis (e.g., ENU, Rathkolb et al., *Exp. Physiol.*, 85(6):635-644, 2000), and the tetracycline-regulated gene expression system (e.g., U.S. Pat. No. 6,242,667). The term "gene" as used herein includes any part of a gene, i.e., regulatory sequences, promoters, enhancers, exons, introns, coding sequences, etc. The nucleic acid present in the construct or transgene can be naturally-occurring wild-type, polymorphic, or mutated.

Along these lines, polynucleotides of the present invention can be used to create transgenic animals, e.g. a non-human animal, comprising at least one cell whose genome comprises a functional disruption of a differentially-regulated gene. By the phrases "functional disruption" or "functionally disrupted," it is meant that the gene does not express a biologically-active product. It can be substantially deficient in at least one functional activity coded for by the gene. Expression of a polypeptide can be substantially absent, i.e., essentially undetectable amounts are made. However, polypeptide can also be made, but which is deficient in activity, e.g., where only an amino-terminal portion of the gene product is produced.

The transgenic animal can comprise one or more cells. When substantially all its cells contain the engineered gene, it can be referred to as a transgenic animal "whose genome comprises" the engineered gene. This indicates that the endogenous gene loci of the animal has been modified and substantially all cells contain such modification.

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Functional disruption of the gene can be accomplished in any effective way, including, e.g., introduction of a stop codon into any part of the coding sequence such that the resulting polypeptide is biologically inactive (e.g., because it lacks a catalytic domain, a ligand binding domain, etc.), introduction of a mutation into a promoter or other regulatory sequence that is effective to turn it off, or reduce transcription of the gene, insertion of an exogenous sequence into the gene which inactivates it (e.g., which disrupts the production of a biologically-active polypeptide or which disrupts the promoter or other transcriptional machinery), deletion of sequences from the a differentially-regulated gene, etc. Examples of transgenic animals having functionally disrupted genes are well known, e.g., as described in U.S. Pat. Nos. 6,239,326, 6,225,525, 6,207,878, 6,194,633, 6,187,992, 6,180,849, 6,177,610, 6,100,445, 6,087,555, 6,080,910, 6,069,297, 6,060,642, 6,028,244, 6,013,858, 5,981,830, 5,866,760, 5,859,314, 5,850,004, 5,817,912, 5,789,654, 5,777,195, and 5,569,824. A transgenic animal which comprises the functional disruption can also be referred to as a "knock-out" animal, since the biological activity of its a differentially-regulated gene has been "knocked-out." Knock-outs can be homozygous or heterozygous.

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For creating functional disrupted genes, and other gene mutations, homologous recombination technology is of special interest since it allows specific regions of the genome to be targeted. Using homologous recombination methods, genes can be specifically-inactivated, specific mutations can be introduced, and exogenous sequences can be introduced at specific sites. These methods are well known in the art, e.g., as described in the patents above. See, also, Robertson, *Biol. Reproduc.*, 44(2):238-245, 1991. Generally, the genetic engineering is performed in an embryonic stem (ES) cell, or other pluripotent cell line (e.g., adult stem cells, EG cells), and that genetically-modified cell (or nucleus) is used to create a whole organism. Nuclear transfer can be used in combination with homologous recombination technologies.

For example, a differentially-regulated gene locus can be disrupted in mouse ES cells using a positive-negative selection method (e.g., Mansour et al., *Nature*, 336:348-352, 1988). In this method, a targeting vector can be constructed which comprises a part of the gene to be targeted. A selectable marker, such as neomycin resistance genes, can be inserted into a a differentially-regulated gene exon present in the targeting vector, disrupting it. When the vector recombines with the ES cell genome, it disrupts the function of the gene. The presence in the cell of the vector can be determined by expression of neomycin resistance. See, e.g., U.S. Pat. No. 6,239,326. Cells having at least one functionally disrupted gene can

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be used to make chimeric and germline animals, e.g., animals having somatic and/or germ cells comprising the engineered gene. Homozygous knock-out animals can be obtained from breeding heterozygous knock-out animals. See, e.g., U.S. Pat. No. 6,225,525.

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A transgenic animal, or animal cell, lacking one or more functional differentially-regulated genes can be useful in a variety of applications, including, as an animal model for cancer, for drug screening assays, as a source of tissues deficient in said gene activity, and any of the utilities mentioned in any issued U.S. Patent on transgenic animals, including, U.S. Pat. Nos. 6,239,326, 6,225,525, 6,207,878, 6,194,633, 6,187,992, 6,180,849, 6,177,610, 6,100,445, 6,087,555, 6,080,910, 6,069,297, 6,060,642, 6,028,244, 6,013,858, 5,981,830, 5,866,760, 5,859,314, 5,850,004, 5,817,912, 5,789,654, 5,777,195, and 5,569,824.

The present invention also relates to non-human, transgenic animal whose genome comprises recombinant a differentially-regulated gene nucleic acid operatively linked to an expression control sequence effective to express said coding sequence, e.g., in prostate. such a transgenic animal can also be referred to as a "knock-in" animal since an exogenous gene has been introduced, stably, into its genome.

A recombinant a differentially-regulated gene nucleic acid refers to a gene which has been introduced into a target host cell and optionally modified, such as cells derived from animals, plants, bacteria, yeast, etc. A recombinant a differentially-regulated gene includes completely synthetic nucleic acid sequences, semi-synthetic nucleic acid sequences, sequences derived from natural sources, and chimeras thereof. "Operable linkage" has the meaning used through the specification, i.e., placed in a functional relationship with another nucleic acid. When a gene is operably linked to an expression control sequence, as explained above, it indicates that the gene (e.g., coding sequence) is joined to the expression control sequence (e.g., promoter) in such a way that facilitates transcription and translation of the coding sequence. As described above, the phrase "genome" indicates that the genome of the cell has been modified. In this case, the recombinant a differentially-regulated gene has been stably integrated into the genome of the animal. The a differentially-regulated gene nucleic acid in operable linkage with the expression control sequence can also be referred to as a construct or transgene.

Any expression control sequence can be used depending on the purpose. For instance, if selective expression is desired, then expression control sequences which limit its expression can be selected. These include, e.g., tissue or cell-specific promoters, introns, enhancers, etc. For various methods of cell and tissue-specific expression, see, e.g., U.S. Pat.

Nos. 6,215,040, 6,210,736, and 6,153,427. These also include the endogenous promoter, i.e., the coding sequence can be operably linked to its own promoter. Inducible and regulatable promoters can also be utilized.

The present invention also relates to a transgenic animal which contains a functionally disrupted and a transgene stably integrated into the animals genome. Such an animal can be constructed using combinations any of the above- and below-mentioned methods. Such animals have any of the aforementioned uses, including permitting the knock-out of the normal gene and its replacement with a mutated gene. Such a transgene can be integrated at the endogenous gene locus so that the functional disruption and "knock-in" are carried out in the same step.

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In addition to the methods mentioned above, transgenic animals can be prepared according to known methods, including, e.g., by pronuclear injection of recombinant genes into pronuclei of 1-cell embryos, incorporating an artificial yeast chromosome into embryonic stem cells, gene targeting methods, embryonic stem cell methodology, cloning methods, nuclear transfer methods. See, also, e.g., U.S. Patent Nos. 4,736,866; 4,873,191; 4,873,316; 5,082,779; 5,304,489; 5,174,986; 5,175,384; 5,175,385; 5,221,778; Gordon et al., Proc. Natl. Acad. Sci., 77:7380-7384, 1980; Palmiter et al., Cell, 41:343-345, 1985; Palmiter et al., Ann. Rev. Genet., 20:465-499, 1986; Askew et al., Mol. Cell. Bio., 13:4115-4124, 1993; Games et al. Nature, 373:523-527, 1995; Valancius and Smithies, Mol. Cell. Bio., 11:1402-1408, 1991; Stacey et al., Mol. Cell. Bio., 14:1009-1016, 1994; Hasty et al., Nature, 350:243-246, 1995; Rubinstein et al., Nucl. Acid Res., 21:2613-2617,1993; Cibelli et al., Science, 280:1256-1258, 1998. For guidance on recombinase excision systems, see, e.g., U.S. Pat. Nos. 5,626,159, 5,527,695, and 5,434,066. See also, Orban, P.C., et al., "Tissueand Site-Specific DNA Recombination in Transgenic Mice," Proc. Natl. Acad. Sci. USA, 89:6861-6865 (1992); O'Gorman, S., et al., "Recombinase-Mediated Gene Activation and Site-Specific Integration in Mammalian Cells," Science, 251:1351-1355 (1991); Sauer, B., et al., "Cre-stimulated recombination at loxP-Containing DNA sequences placed into the mammalian genome," Polynucleotides Research, 17(1):147-161 (1989); Gagneten, S. et al. (1997) Nucl. Acids Res. 25:3326-3331; Xiao and Weaver (1997) Nucl. Acids Res. 25:2985-2991; Agah, R. et al. (1997) J. Clin. Invest. 100:169-179; Barlow, C. et al. (1997) Nucl. Acids Res. 25:2543-2545; Araki, K. et al. (1997) Nucl. Acids Res. 25:868-872; Mortensen, R. N. et al. (1992) Mol. Cell. Biol. 12:2391-2395 (G418 escalation method); Lakhlani, P. P. et al. (1997) Proc. Natl. Acad. Sci. USA 94:9950-9955 ("hit and run"); Westphal and Leder

(1997) Curr. Biol. 7:530-533 (transposon-generated "knock-out" and "knock-in"); Templeton, N. S. et al. (1997) Gene Ther. 4:700-709 (methods for efficient gene targeting, allowing for a high frequency of homologous recombination events, e.g., without selectable markers); PCT International Publication WO 93/22443 (functionally-disrupted).

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A polynucleotide according to the present invention can be introduced into any non-human animal, including a non-human mammal, mouse (Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1986), pig (Hammer et al., Nature, 315:343-345, 1985), sheep (Hammer et al., Nature, 315:343-345, 1985), cattle, rat, or primate. See also, e.g., Church, 1987, Trends in Biotech. 5:13-19; Clark et al., Trends in Biotech. 5:20-24, 1987); and DePamphilis et al., BioTechniques, 6:662-680, 1988. Transgenic animals can be produced by the methods described in U.S. Pat. No. 5,994,618, and utilized for any of the utilities described therein.

### Database

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The present invention also relates to electronic forms of polynucleotides, polypeptides, etc., of the present invention, including computer-readable medium (e.g., magnetic, optical, etc., stored in any suitable format, such as flat files or hierarchical files) which comprise such sequences, or fragments thereof, e-commerce-related means, etc. Along these lines, the present invention relates to methods of retrieving gene sequences from a computer-readable medium, comprising, one or more of the following steps in any effective order, e.g., selecting a cell or gene expression profile, e.g., a profile that specifies that said gene is differentially expressed in prostate cancer, and retrieving said differentially expressed gene sequences, where the gene sequences consist of the genes represented by Tables 1 and 2.

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A "gene expression profile" means the list of tissues, cells, etc., in which a defined gene is expressed (i.e, transcribed and/or translated). A "cell expression profile" means the genes which are expressed in the particular cell type. The profile can be a list of the tissues in which the gene is expressed, but can include additional information as well, including level of expression (e.g., a quantity as compared or normalized to a control gene), and information on temporal (e.g., at what point in the cell-cycle or developmental program) and spatial expression. By the phrase "selecting a gene or cell expression profile," it is meant that a user decides what type of gene or cell expression pattern he is interested in retrieving, e.g., he may require that the gene is differentially expressed in a tissue, or he may require that the

gene is not expressed in blood, but must be expressed in prostate cancer. Any pattern of expression preferences may be selected. The selecting can be performed by any effective method. In general, "selecting" refers to the process in which a user forms a query that is used to search a database of gene expression profiles. The step of retrieving involves searching for results in a database that correspond to the query set forth in the selecting step. Any suitable algorithm can be utilized to perform the search query, including algorithms that look for matches, or that perform optimization between query and data. The database is information that has been stored in an appropriate storage medium, having a suitable computer-readable format. Once results are retrieved, they can be displayed in any suitable format, such as HTML.

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For instance, the user may be interested in identifying genes that are differentially expressed in a prostate cancer. He may not care whether small amounts of expression occur in other tissues, as long as such genes are not expressed in peripheral blood lymphocytes. A query is formed by the user to retrieve the set of genes from the database having the desired gene or cell expression profile. Once the query is inputted into the system, a search algorithm is used to interrogate the database, and retrieve results.

### Advertising, licensing, etc., methods

The present invention also relates to methods of advertising, licensing, selling, purchasing, brokering, etc., genes, polynucleotides, specific-binding partners, antibodies, etc., of the present invention. Methods can comprises, e.g., displaying a a differentially-regulated gene gene, a differentially-regulated gene polypeptide, or antibody specific for a differentially-regulated gene in a printed or computer-readable medium (e.g., on the Web or Internet), accepting an offer to purchase said gene, polypeptide, or antibody.

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# Other

A polynucleotide, probe, polypeptide, antibody, specific-binding partner, etc., according to the present invention can be isolated. The term "isolated" means that the material is in a form in which it is not found in its original environment or in nature, e.g., more concentrated, more purified, separated from component, etc. An isolated polynucleotide includes, e.g., a polynucleotide having the sequenced separated from the chromosomal DNA found in a living animal, e.g., as the complete gene, a transcript, or a cDNA. This polynucleotide can be part of a vector or inserted into a chromosome (by

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specific gene-targeting or by random integration at a position other than its normal position) and still be isolated in that it is not in a form that is found in its natural environment. A polynucleotide, polypeptide, etc., of the present invention can also be substantially purified. By substantially purified, it is meant that polynucleotide or polypeptide is separated and is essentially free from other polynucleotides or polypeptides, i.e., the polynucleotide or polypeptide is the primary and active constituent. A polynucleotide can also be a recombinant molecule. By "recombinant," it is meant that the polynucleotide is an arrangement or form which does not occur in nature. For instance, a recombinant molecule comprising a promoter sequence would not encompass the naturally-occurring gene, but would include the promoter operably linked to a coding sequence not associated with it in nature, e.g., a reporter gene, or a truncation of the normal coding sequence.

The term "marker" is used herein to indicate a means for detecting or labeling a target. A marker can be a polynucleotide (usually referred to as a "probe"), polypeptide (e.g., an antibody conjugated to a detectable label), PNA, or any effective material.

The topic headings set forth above are meant as guidance where certain information can be found in the application, but are not intended to be the only source in the application where information on such topic can be found.

#### Reference materials

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For other aspects of the polynucleotides, reference is made to standard textbooks of molecular biology. See, e.g., Hames et al., <u>Polynucleotide Hybridization</u>, IL Press, 1985; Davis et al., <u>Basic Methods in Molecular Biology</u>, Elsevir Sciences Publishing, Inc., New York, 1986; Sambrook et al., <u>Molecular Cloning</u>, CSH Press, 1989; Howe, <u>Gene Cloning and Manipulation</u>, Cambridge University Press, 1995; Ausubel et al., <u>Current Protocols in Molecular Biology</u>, John Wiley & Sons, Inc., 1994-1998.

The preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limiting the remainder of the disclosure in any way whatsoever. The entire disclosure of all applications, patents and publications, cited above and in the figures are hereby incorporated by reference in their entirety.

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#### Claims:

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1. A method for diagnosing a prostate cancer in a sample comprising prostate tissue, comprising:

determining the number of target genes which are differentially-regulated in said sample, wherein said target genes are selected from SEQ ID NO 1-211 of claim 26, whereby said number is indicative of the probability that said sample comprises prostate cancer.

- A method of claim 1, wherein said determining is performed by Northern
   blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or in situ hybridization using polynucleotide probes specific for genes selected from SEQ ID NO 1-211 of claim 26.
  - 3. A method of claim 1, wherein said determining is performed by: contacting said sample with a polynucleotide probe under conditions effective for said probe to hybridize specifically to a target nucleic acid in said sample, and detecting the amount of hybridization between said probe and target nucleic acid, and

comparing the amount of hybridization in said sample with the amount of hybridization of said probe in a second sample comprising normal prostate tissue.

4. A method of claim 1, wherein said determining is performed by: contacting said sample with a polynucleotide probe under conditions effective for said probe to hybridize specifically to a target nucleic acid in said sample, and detecting the amount of hybridization between said probe and target nucleic acid,

detecting the amount of hybridization between said probe and target nucleic acid

comparing the amount of hybridization in said sample with the amount of hybridization between a second probe and its corresponding second target nucleic acid in said sample.

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- 5. A method of clam 2, wherein said probe is a contiguous sequence of at least 8 nucleotides selected from a polynucleotide sequence selected from SEQ ID NOS 1-107 of claim 26, or a complement thereto.
- 5 6. A method of assessing a therapeutic or preventative intervention in a subject having a prostate cancer, comprising,

determining the expression levels in a sample comprising prostate tissue of target genes which are differentially-regulated in prostate cancer,

wherein said target genes are selected from SEQ ID NO 1-211 of claim 26.

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- 7. A method of claim 6, wherein the expression levels of at least 10 genes are determined.
- 8. A method of claim 6, wherein the determining is performed by Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or in situ hybridization using polynucleotide probes specific for genes selected from SEQ IDS NO 1-211 of claim 26.
- 9. A method for identifying agents that modulate the expression of target polynucleotides differentially-regulated in prostate cancer cells, comprising,

contacting a prostate cell population with a test agent under conditions effective for said test agent to modulate the expression of a target polynucleotide in said cell population, and

- determining whether said test agent modulates said target polynucleotide expression, wherein said target polynucleotide is selected from SEQ ID NOS 1-107 of claim 26.
  - 10. A method of claim 9, wherein said agent is an antisense polynucleotide to said target polynucleotide sequence and which is effective to inhibit translation of said target polynucleotide.

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11. A method for identifying agents that modulate a biological activity of a polypeptide differentially-regulated in prostate cancer cells, comprising,

contacting a polypeptide differentially-regulated in prostate cancer cells with a test agent under conditions effective for said test agent to modulate a biological activity of said polypeptide, and

determining whether said test agent modulates said biological activity, wherein said polypeptide is selected from SEQ ID NOS 108-211 of claim 26.

- 12. A method of treating prostate cancer, comprising,
- administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of at least one sequence selected from SEQ ID NOS 1-211 of claim 26.
- 13. A method of claim 12, wherein said agent is an antibody or an antisense which is effective to inhibit translation of said gene.
  - 14. A method of diagnosing a prostate cancer comprising:

assessing the expression of at least one gene selected from SEQ ID NO 1-211 of claim 26, wherein said gene is differentially-regulated in said cancer.

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15. A method of claim 14, wherein assessing is:

measuring mRNA expression levels of said or measuring the expression levels of polypeptide coded for by said gene.

25 16. A method of claim 14, further comprising:

comparing said expression to the expression of said polynucleotide in a known normal tissue.

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- 17. A method of claim 14, wherein said assessing detecting is performed by: Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization, and
- using a polynucleotide probe specific for a polynucleotide sequence selected from SEQ ID NOS 1-107 of claim 26.
  - 18. A method of claim 14, wherein the expression of at least one up-regulated polynucleotide and at least one down-regulated polynucleotide are assessed.
- 19. A method of claim 14, wherein the expression of at least five up-regulated polynucleotides and at least five down-regulated polynucleotides are assessed.
  - 20. A method of retrieving prostate cancer differentially-regulated gene sequences from a computer-readable medium, comprising:

selecting a gene expression profile that specifies that said gene is differentiallyregulated in a prostate cancer, and retrieving prostate cancer differentially-regulated gene sequences,

where the gene sequences consist of genes selected from SEQ ID NO 1-211 of claim 26.

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21. An ordered array of polynucleotide probes for detecting the expression of differentially-regulated prostate cancer genes in a sample, comprising:

polynucleotide probes associated with a solid support, wherein each probe is specific for a different differentially-regulated prostate cancer gene, and the probes are specific for genes selected from SEQ ID NO 1-211 of claim 26.

22. An array of claim 21, wherein said array comprises probes specific for upregulated and down-regulated polynucleotides.

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23. A method of advertising for sale, commercial use, or licensing, comprising: displaying at least one polynucleotide or polypeptide sequence selected from

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SEQ ID NO 1-211 of claim 26, or a complement thereto.

- 24. A non-human, transgenic mammal having a functional disruption in at least one gene selected from SEQ ID NO 1-211 of claim 26, and which is susceptible to prostate cancer.
- 25. A cell expression profile consisting of the expression pattern of a prostate cancer tissue sample for differentially-regulated genes of claim 26.
- 26. A plurality of genes which are differentially regulated in a prostate cancer, selected from:

up-regulated genes having SEQ ID NOS 1-75 and 140-211; and down-regulated genes having SEQ ID 76-107 and 108-139.

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19. ELUI DI INSTITUTO DE LA SONDA HUMBESZAA Human ribosomal protein S24 mRNA. Lean shame and bascaption           21. VIA DI COSCISSATIO UN STATEM HUMBESZAA Human ribosomal protein S24 mRNA. Lean shame and bascaption of the statement of the statement of the statement and bascaption of the statement of	DNA SEO	Prt	L			
141 PC010849U U 142 PC010839U U 143 PC010839U U 144 PC020728U U 146 PC020732U U 147 PC011348U U 148 PC040373U U 149 PC04039U U 140 PC04039U U 150 PC04044U U 151 PC04044U U 152 PC051210U U 153 PC05029U U 154 PC05029U U 155 PC05029U U 156 PC06043U U 157 PC06043U U 167 PC06043U U 168 PC07052U U 169 PC07053U U 161 PC06043U U 162 PC06043U U 163 PC06043U U 164 PC06043U U 165 PC06043U U 167 PC06043U U 167 PC06043U U 168 PC07053U U 169 PC07053U U 169 PC07053U U 169 PC07053U U 170 PC06147U U 171 PC06043U U 172 PC06147U U 173 PC06183U U 174 PC06183U U 175 PC06183U U 177 PC06084U U 177 PC08081U U 177 PC08081U U 178 PC07089U U 178 PC07089U U 178 PC07089U U 179 PC07089U U	2	25 DEC 10	DC03003111	<u> </u>		WIMPDC24A Himan ribosomal nortein C24 mBNA
142 PC010839U U 143 PC010957U U 144 PC020728U U 145 PC011342U U 146 PC020732U U 147 PC011348U U 148 PC040132U U 149 PC040132U U 149 PC040132U U 150 PC040132U U 151 PC04044U U 152 PC051210U U 153 PC050209U U 154 PC050209U U 155 PC050209U U 156 PC050131U U 157 PC05044U U 158 PC050209U U 158 PC050209U U 159 PC050209U U 159 PC050209U U 150 PC060441U U 150 PC060441U U 151 PC060441U U 161 PC060441U U 162 PC070132U U 163 PC050209U U 164 PC060441U U 165 PC070132U U 166 PC070132U U 167 PC060171U U 177 PC060177U U 177 PC060183U U 177 PC090842U U	2	14	PC010849U	حاد	3978243	AFORM 4 Through International Programmer Aformation and Aformation
143 PC010957U U 144 PC020728U U 145 PC021342U U 146 PC020732U U 147 PC041029U U 148 PC040132U U 148 PC040132U U 150 PC040158U U 151 PC040418U U 152 PC051210U U 153 PC05029U U 154 PC05029U U 155 PC05029U U 156 PC050131U U 157 PC050209U U 158 PC050209U U 158 PC050209U U 158 PC050209U U 159 PC050209U U 158 PC050209U U 159 PC05043U U 161 PC060441U U 162 PC060441U U 163 PC060441U U 164 PC060441U U 165 PC060441U U 166 PC060441U U 167 PC060430U U 168 PC060430U U 168 PC070534U U 169 PC070534U U 170 PC061179U U 171 PC060130U U 172 PC061179U U 173 PC061830U U 174 PC060842U U 175 PC08051U U 177 PC090842U U 177 PC090842U U 178 PC091089U U 177 PC090842U U 178 PC091089U U 178 PC091089U U 179 PC071089U U 179 PC071089U U	e.	142	PC010839U	٥	6912451	NM 012289.11 Homo sapiens Kelch-like ECH-associated protein 1 (KIAA0132).
144 PC020728U U 145 PC021342U U 146 PC030732U U 147 PC041039U U 148 PC030732U U 148 PC030732U U 149 PC050853U U 150 PC040158U U 151 PC040441U U 152 PC05029EU U 154 PC05029EU U 155 PC050151U U 156 PC050151U U 157 PC050202U U 158 PC05043U U 158 PC05043U U 159 PC05043U U 169 PC060441U U 161 PC060441U U 161 PC060441U U 162 PC060441U U 163 PC050202U U 164 PC060441U U 165 PC06043U U 166 PC06043U U 167 PC06043U U 167 PC06043U U 168 PC07034U U 177 PC06043U U 178 PC07089U U 178 PC07089U U 178 PC07089U U 179 PC07089U U	4	143	PC010957U	5	4557844	NM 001034.1 Homo sapiens ribonucleotide reductase M2 polypeptide (RRM2) mRNA
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PC011348U U 147 PC041029U U 148 PC0400372U U 148 PC0400372U U 150 PC040158U U 151 PC040158U U 152 PC051210U U 152 PC051210U U 153 PC050151U U 154 PC050296U U 155 PC050151U U 156 PC050151U U 157 PC052095U U 158 PC050030U U 158 PC050030U U 159 PC050474U U 160 PC041980U U 161 PC060441U U 162 PC060441U U 163 PC060441U U 164 PC060441U U 165 PC060441U U 167 PC060441U U 167 PC060441U U 168 PC070544U U 168 PC070541U U 169 PC070541U U 167 PC060471U U 167 PC060471U U 167 PC060471U U 168 PC070541U U 168 PC070541U U 169 PC070541U U 177 PC060470U U 177 PC060470U U 177 PC060470U U 177 PC060830U U 177 PC060830U U 177 PC060830U U 177 PC090842U U 178 PC091058U U 178 PC091058U U 179 PC091058U U 177 PC090842U U 178 PC0910780U U	_	146	PC030732U	5	4504374	Homo sapiens H factor 1 (complement) (HF1) mRNA
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150 PC040158U U 151 PC040441U U 152 PC05130U U 153 PC05131U U 155 PC050151U U 155 PC050151U U 156 PC050151U U 157 PC05020U U 158 PC050020U U 159 PC050020U U 159 PC050020U U 160 PC041338U U 161 PC041338U U 161 PC041338U U 162 PC060441U U 163 PC060441U U 164 PC060441U U 165 PC060441U U 166 PC070348U U 167 PC060441U U 168 PC070348U U 169 PC070349U U 170 PC061477U U 171 PC060940U U 172 PC061379U U 173 PC061821U U 174 PC060842U U 175 PC061821U U 177 PC060842U U 177 PC060842U U 178 PC08051U U 178 PC08051U U 178 PC08051U U 179 PC070890U U 177 PC080841U U 177 PC080842U U 177 PC080842U U 177 PC080842U U 178 PC070890U U 178 PC070890U U 179 PC070890U U 179 PC070890U U	=	149	PC050853U	_	4503724	NM 000801.1  Homo sapiens FK506-binding protein 1A (12kD) (FKBP1A) mRNA
151 PC040441U U 152 PC051210U U 153 PC050139U U 155 PC050151U U 156 PC050151U U 157 PC052095U U 158 PC052095U U 158 PC052095U U 159 PC050209U U 161 PC041338U U 161 PC041338U U 162 PC060474U U 163 PC060474U U 164 PC060431U U 165 PC060431U U 165 PC060431U U 167 PC060431U U 168 PC070544U U 167 PC060430U U 167 PC060430U U 177 PC060830U U 177 PC060830U U 177 PC061839U U 177 PC071851U U	12	150	PC040158U	∍	4826949	Homo sapiens kaliikrein 7 (chymotryptic stratum comeum) (KLK7) mRNA
152 PC051210U U 154 PC050296U U 155 PC050151U U 156 PC050151U U 157 PC0502095U U 158 PC0502095U U 158 PC0502095U U 158 PC0502091 U 169 PC050474U U 161 PC0614319 U 162 PC060471U U 164 PC060471U U 165 PC060471U U 166 PC060471U U 167 PC060471U U 167 PC060471U U 168 PC070544U U 167 PC060471U U 168 PC070541U U 170 PC061471U U 171 PC061471U U 172 PC061471U U 173 PC061471U U 174 PC061832U U 175 PC061832U U 177 PC060839U U 177 PC070830U U 177 PC070830U U 177 PC070830U U	13	151	PC040441U	2	4826879	Homo sapiens oxidase (cytochrome c) assembly 1-like (OXA1L) mRNA
154 PC050296U U 155 PC050151U U 156 PC050151U U 157 PC052095U U 158 PC052095U U 159 PC052095U U 159 PC052095U U 160 PC041338U U 161 PC041338U U 162 PC060431U U 163 PC060431U U 164 PC060441U U 165 PC060431U U 166 PC060431U U 166 PC060431U U 167 PC0601477U U 168 PC070343U U 170 PC061477U U 171 PC0601471U U 172 PC061471U U 173 PC061830U U 174 PC060841U U 175 PC090842U U 177 PC090842U U	4	152	PC051210U	5	4506056	NM 002731.1 Homo sapiens protein kinase, cAMP-dependent, catalytic, beta
155 PC050151U U 156 PC050149U U 157 PC052095U U 158 PC052095U U 159 PC052095U U 159 PC051338U U 160 PC041338U U 161 PC04138U U 162 PC060443U U 163 PC060443U U 164 PC060441U U 165 PC060441U U 165 PC060441U U 166 PC060529U U 166 PC060529U U 167 PC060441U U 167 PC060441U U 168 PC070534U U 170 PC061477U U 171 PC060940U U 172 PC061839U U 173 PC061839U U 174 PC060842U U 175 PC08054U U 177 PC08081U U 177 PC08081U U 178 PC08055U U 177 PC08081U U 178 PC08055U U 177 PC08081U U 178 PC08051U U 177 PC08081U U	15	154	PC050296U	5	5453633	Homo sapiens dynein cytoplasmic light intermediate polypeptide 2 (DNCLI2) mRNA
156 PC050149U U 157 PC052095U U 158 PC052095U U 158 PC052029U U 159 PC050050U U 160 PC041338U U 161 PC04138U U 162 PC060471U U 163 PC060471U U 164 PC060471U U 165 PC070152U U 166 PC070534U U 167 PC06041U U 168 PC07054U U 169 PC07054U U 170 PC061477U U 171 PC060940U U 172 PC061827U U 173 PC061821U U 174 PC060871U U 175 PC08051U U 177 PC060871U U 177 PC060872U U 177 PC060872U U 177 PC060872U U 178 PC07089U U 178 PC07089U U 179 PC07089U U 177 PC07089U U	16	155	PC050151U	5	6715599	NM 002078.2] Homo sapiens golgi autoantigen, golgin subfamily a, 4
157 PC052095U U 158 PC052095U U 159 PC052029U U 161 PC041338U U 161 PC041338U U 162 PC060443U U 163 PC060443U U 164 PC060443U U 165 PC060441U U 166 PC060529U U 166 PC060529U U 167 PC06044U U 167 PC06044U U 167 PC06143U U 177 PC06044U U 177 PC06040U U 177 PC06040U U 177 PC06040U U 177 PC061839U U 177 PC06051U U 177 PC07089U U 177 PC07089U U 177 PC07089U U	17	156	PC050149U	_	2217930	AB004884 Homo sapiens mRNA for PKU-alpha,
158 PC052029U U 169 PC050209U U 161 PC041338U U 161 PC041380U U 162 PC060474U U 163 PC060431 U 164 PC060431 U 165 PC060431 U 166 PC06059U U 167 PC06039U U 167 PC060340U U 168 PC070544U U 168 PC070541U U 167 PC061477U U 177 PC061479U U 177 PC06183U U 177 PC07089U U	18	157	PC052095U	_	641957	HUMMYOHCB Human nonmuscle myosin heavy chain-B (MYH10) mRNA partial cds
159 PC050620U U 160 PC041338U U 161 PC041938U U 162 PC06043U U 163 PC06043U U 164 PC06043U U 166 PC06038U U 166 PC060348U U 166 PC070534U U 167 PC060348U U 168 PC07054U U 170 PC061477U U 171 PC060940U U 172 PC061839U U 173 PC061839U U 174 PC061839U U 175 PC061839U U 177 PC06083U U 177 PC08091U U 177 PC090754U U	19	158	PC052029U	2	5803218	Homo sapiens serine protease inhibitor Kazal type 5 (SPINKS) mRNA
160 PCO41338U U 161 PCO41938U U 161 PCO6498U U 163 PCO60443U U 164 PCO60441U U 165 PCO70152U U 166 PC06053U U 166 PC070534U U 166 PC070534U U 167 PC061477U U 170 PC061477U U 171 PC06084U U 172 PC06183U U 174 PC06183U U 175 PC06183U U 177 PC06081U U 177 PC06081U U 177 PC08081U U 178 PC08081U U 177 PC08081U U 177 PC08081U U 178 PC08081U U 177 PC08081U U	20	159	PC050620U	n	4504580	NM_003641.1  Homo sapiens interferon Induced transmembrane protein 1, (IFITM1), mRNA
161 PC041980U U 162 PC060474U U 163 PC060443U U 164 PC060443U U 165 PC070152U U 166 PC060529U U 166 PC060529U U 167 PC060348U U 168 PC070343U U 170 PC061477U U 171 PC060940U U 172 PC061839U U 174 PC0601839U U 175 PC061839U U 177 PC0601839U U 178 PC061839U U 178 PC0701839U U 178 PC0701839U U 179 PC0701839U U 177 PC070899U U 177 PC070890U U 177 PC070890U U 177 PC070890U U 177 PC070890U U	21	160	PC041338U	D	8051620	Homo sapiens 2'5'-oligoadenylate synthetase 1 (OAS1) transcript variant E18 mRNA
162 PC060474U U 163 PC060443U U 164 PC060443U U 165 PC070152U U 166 PC060529U U 167 PC080348U U 168 PC070544U U 169 PC070343U U 170 PC061477U U 171 PC060801 U 171 PC0608179U U 172 PC061779U U 173 PC061839U U 174 PC061821U U 175 PC080511U U 177 PC080542U U	22	161	PC041980U	a	6735451	HSA271091 Homo sapiens mRNA for B-ind1 protein (B-ind1 gene)
163 PC060443U U 164 PC060441U U 165 PC060529U U 166 PC060529U U 167 PC060348U U 168 PC070544U U 169 PC070343U U 170 PC061477U U 171 PC06040U U 173 PC061779U U 174 PC061839U U 175 PC061839U U 177 PC06083U U 177 PC06083U U 177 PC06083U U 177 PC08051U U 177 PC08051U U 177 PC08051U U 177 PC08081U U	23	162	PC060474U	n	4759321	Homo sapiens wingless-type MMTV integration site family member 2B (WNT2B) mRNA
164 PC060441U U 165 PC070152U U 167 PC060348U U 168 PC070544U U 169 PC070544U U 170 PC061477U U 171 PC060940U U 172 PC061477U U 173 PC061839U U 174 PC061839U U 175 PC061839U U 177 PC060830U U 177 PC08051U U 177 PC08051U U 177 PC08051U U 177 PC08051U U 177 PC090754U U	24	163	PC060443U	n	4506730	Homo sapiens ribosomal protein S6 (RPS6) mRNA
166 PC070152U U 166 PC060529U U 167 PC060539U U 168 PC070544U U 169 PC070544U U 170 PC061477U U 171 PC060147U U 172 PC061839U U 174 PC061839U U 175 PC06182U U 177 PC090542U U 177 PC090542U U 177 PC090754U U 177 PC090754U U 177 PC090754U U 177 PC090754U U 177 PC090842U U	25	164	PC060441U	n	1688257	HSU78045 Human collagenase and stromelysin genes, complete cds, and metalloelastase gene, partial cds
166 PC060529U U 167 PC080348U U 168 PC070544U U 169 PC070343U U 170 PC061477U U 171 PC060940U U 172 PC061839U U 174 PC061837U U 175 PC08182TU U 175 PC08051U U 176 PC08051U U 177 PC08051U U	26	165	PC070152U	Э	4506712	Homo sapiens ribosomal protein S27a (RPS27A) mRNA
167 PC060348U U 168 PC070544U U 169 PC070343U U 171 PC06137U U 172 PC061779U U 173 PC061839U U 174 PC061839U U 175 PC080511U U 176 PC08051U U 177 PC080542U U	27	166	PC060529U	_	4503820	Homo sapiens FYN-binding protein (FYB-120130) (FYB) mRNA and translated products
168 PC070544U U 169 PC070343U U 170 PC060447U U 171 PC060347U U 172 PC061779U U 173 PC061839U U 174 PC061827U U 175 PC080511U U 176 PC08051U U 177 PC080842U U	28	167	PC080348U	_	9623360	AF261688 Homo sapiens DNA polymerase epsilon p12 subunit gene, complete cds
169 PC070343U U 170 PC061477U U 171 PC060390U U 173 PC061839U U 174 PC061827U U 175 PC080511U U 176 PC08051U U 177 PC08042U U 177 PC09042U U	29	168	PC070544U	2	1679960	S42658 S3 ribosomal protein (human colon mRNA 826 nt)
170 PC061477U U 171 PC060940U U 172 PC06179U U 173 PC061839U U 174 PC061827U U 175 PC080511U U 177 PC090754U U 177 PC090728U U 177 PC09082U U 177 PC07083U U	30	169	PC070343U	٦.	4507210	Homo sapiens signal recognition particle 14kD (homologous Alu RNA-binding protein) (SRP14) mRNA
171 PC060940U U 172 PC061779U U 173 PC061839U U 174 PC08182TU U 175 PC090754U U 177 PC090754U U 177 PC090754U U 177 PC09082U U 177 PC09082U U 177 PC07083U U 177 PC07083U U	31	170	PC061477U	_	4506386	Homo sapiens RAD23 (S. cerevisiae) homolog B (RAD23B) mRNA
172 PC061779U U 173 PC061839U U 174 PC061839U U 175 PC090851U U 176 PC090842U U 177 PC090842U U 178 PC091028U U 179 PC071851U U PC071851U U	32	17	PC060940U	_	5052074	Homo sapiens PAPS synthetase-2 (PAPSS2) mRNA
173 PC061839U U 174 PC061827U U 175 PC080511U U 177 PC090842U U 178 PC091028U U 178 PC091028U U 178 PC091028U U 179 PC071851U U PC071851U U	33	172	PC061779U	_	4504766	Homo sapiens integrin beta 1 (fibronectin receptor beta polypeptide antigen CD29 includes MDF2 MSK12) (ITGB1) mRNA
174 PC061827U U 175 PC08051U U 176 PC090754U U 177 PC090842U U 178 PC091028U U PC070890U U PC071851U U PC071851U U	34		PC061839U	_	8394498	Homo sapiens ubiquitin associated protein (UBAP) mRNA
175 PC080511U U 176 PC080542U U 177 PC080842U U 178 PC091028U U PC071028U U PC071028U U PC071851U U PC071851U U	35		I PC061827U	_	7382495	Homo sapiens p21Cdc42Rac1-activated kinase 1 (yeast Ste20-related) (PAK1) mRNA
176 PC090754U U 177 PC090842U U 178 PC091028U U PC070890U U PC071851U U	36	175	PC080511U	2	4504190	NM 000179.1] Homo sapiens mutS (E. coli) homolog 6 (MSH6),
177 PC090842U U 178 PC091028U U PC070890U U PC071851U U 179 PC070729U U	37		3 PC090754U	D	4503472	Homo sapiens eukaryotic translation elongation factor 1 alpha 1-like 14 (EEF1A1L14) mRNA
178 PC091028U U PC070890U U PC071851U U 179 PC070729U U	38		PC090842U	2	4557031	Homo sapiens lactate dehydrogenase B (LDHB) mRNA
PC070890U U PC071851U U 179 PC070729U U	39	178	PC091028U	_	7662425	Homo sapiens KiAA0976 protein (KiAA0976) mRNA
PC071851U U 179 PC070729U U	40		PC070890U	_	6531675	AF205588.1JAF205588 Homo sapiens ZNF01 and HUMORFKG1B genes
179 PC070729U U	41		PC071851U	_	3090894	AF052497 Homo sapiens clone B18 unknown mRNA
	42		PC070729U	ے	8923790	Homo sapiens rTS beta protein (HSRTSBETA) mRNA

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<u> </u>	153
211 PC020741U V 7657624 NM 014393.1 Homo sapiens staufen (Drosophila, RNA-binding protein) homolog 2	75 211
210 PC121671U   7661635 Homo sapiens DKFZP564O2082 protein (DKFZP564O2082) mRNA	
209 PC120331U   4504424 NM 002128.1 Homo sapiens high-mobility group (nonhistone chromosomal) protein 1	73 209
207 PC11116BU U 4759283 NM 004181.1J Homo sapiens ubiquitin carboxyl-terminal esterase L1	
205 PC091839U   7188646 AF222043 Homo sapiens ubiquitin-associated protein (NAG20) mRNA complete cds	֓֞֞֜֜֜֜֓֓֓֓֓֜֜֜֓֓֓֓֓֡
204 PC092052U U 4505634 Homo sapiens BH-protocadherin (brain-heart) (9999DHT) mRNA	
203 PC091853U U 31091 X16869.1 HSEF1AC Human mRNA for elongation factor 1-alpha	İ
202 PC091888U   4757809   Homo sap/ ATP synthase H+ transporting mito F1 complex alpha subunit isoform 1 cardiac muscle (ATP5A1) nuclear gene	66 202
201 PC092004U 8922823 NM 018300.1I Homo sapiens hypothetical protein FLJ11015 (FLJ11015)	
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197 PC030454U   4506678 Homo sapiens ribosomal protein S10 (RPS10) mRNA	
196[PC030471U]U 31396[HSFIB1 Human mRNA for fibronectin (FN precursor)	
195 PC030247U 348706 HUMCACTHBS Homo sapiens cathepsin B mRNA 3' UTR with a stem-loop structure providing mRNA stability	
194 PC020162U 4507164 NM 003113.11 Homo sapiens nuclear antigen Sp100 (SP100) mRNA	
193 PC020185U 7669502 NM 013995.1 Homo sapiens lysosomal-associated membrane protein 2	
2	
191 PC010337U 6005813 Homo sapiens serine threonine protein kinase (NDR) mRNA	
190 PC010139U   7657203 Homo sapiens acidic 82 kDa protein mRNA (HSU15552) mRNA	54 190 F
189 PC010434U   4505374 NM 002499.1 Homo sapiens neogenin (chicken) homolog 1	
188 PC091425U   4732025 AF118569 Homo sapiens angiotensin I converting enzyme precursor	Ĺ
187 PC101430U   099453 M69199. 1 HUMG0S2A Human G0S2 protein gene, complete cds	
186 PC090625U 7706215 Homo sapiens H-2K binding factor-2 (LOC51580) mRNA	
185/PC101863U/U 35037/HSNFIV H.sapiens mRNA for nuclear factor IV	
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180 PC080742U U 4507186 NM 003125.1 Homo sapiens small proline-rich protein 1B (cornifin)	43 180 P

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9/	801	PC040734D 1D	2	5174656	NM 006096.1 Homo sapiens differentiation-related gene I nickel-specific induction protein
77	109	PC040156D   D	Ω	4505748	Homo sapiens phosphofructokinase muscle (PFKM) mRNA
78	110	PC051745D   D	Q	4758751	Homo sapiens neuronal apoptosis inhibitory protein (NAIP) mRNA
62	111	PC042021D D	a	4505986	Homo sapiens PTPRF interacting protein binding protein 1 (liprin beta 1) (PPFIBP1) mRNA and translated products
08 08	112	PC060144D D	٥	4758199	NM 004415.1  Homo sapiens desmoplakin (DPI, DPII) (DSP) mRNA
81	113	PC080139D	q	7657159	NM 014362.1 Homo sapiens 3-hydroxyisobutyryl-Coenzyme A hydrolase (HIBCH), mRNA
82	114	PC080435D	Q	4758807	Homo sapiens ras GTPase activating protein-like (NGAP) mRNA
83	115	PC070436D	q	9790904	NM 001924.1 Homo sapiens growth arrest and DNA-damage-inducible
84	911	PC061342D	q	186485	HUMINT04 Human leukocyte adhesion protein p15095 alpha subunit gene exons 16 - 21
85	111	PC060793D	a	4507582	NM 000043.1  Homo sapiens tumor necrosis factor receptor superfamily
98	811	PC060743D	a	4557256	Homo sapiens adenylate cyclase 8 (brain) (ADCY8) mRNA
87	119	PC061528D  D	Q	4506700	Homo sapiens ribosomal protein S23 (RPS23) mRNA
88	120	PC090788D	a	5031638	Homo sapiens cornichon-like (CNIL) mRNA
68	121	PC090722D	a	7670747	AF227906 Homo sapiens UDP-glucoseglycoprotein glucosyltransferase 2 precursor mRNA complete cds
8	122	PC071770D	Q	31441	HSFNRB Human mRNA for integrin beta 1 subunit
16	123	PC090677D	q	187701	HUMMHBA123 Human MHC protein homologous to chicken B complex protein mRNA complete cds
26	124	PC101847D	a	5902021	Homo sapiens PL6 protein (PL6) mRNA
93	125	PC090622D	Q	4506858	NM_002997.1J Homo sapiens syndecan 1 (SDC1) mRNA
94	126	PC010433D  D	Q	4827043	Homo sapiens thyroid hormone receptor-associated protein 240 kDa subunit (TRAP240) mRNA
95	127	PC020238D  D	a	4503090	NM 001893.1  Homo sapiens casein kinase 1, delta (CSNK1D) mRNA
96	128	PC030301D D	Q	4506728	Homo sapiens ribosomal protein S5 (RPS5) mRNA
25	129	PC110249D	Q	4759257	Homo sapiens Ac-like transposable element (ALTE) mRNA
86	130	PC110541D	D	5031778	Homo sapiens interferon gamma-inducible protein 16 (IFI16) mRNA
66		PC110431D	Q	3885367	AB019564 Homo sapiens mRNA expressed only in placental villi clone SMAP47
90	131	PC110940D  D	D	4758949	NM 000942.1J Homo sapiens peptidylprolyl isomerase B (cyclophilin B)
101	132	PC111588D [D	a	4503412	Homo sapiens diphtheria toxin receptor (heparin-binding epidermal growth factor-like growth factor) (DTR) mRNA
102	133	PC111669D   D	Q	7705822	Homo sapiens N-terminal acetyltransferase complex ard Isubunit (LOC51126) mRNA
103	134	PC032046D [D	a	7657325	NM 014623.1  Homo sapiens male-enhanced antigen (MEA).
104	135	PC120741D	D	5174388	NM 005891.1  Homo sapiens acetyl-Coenzyme A acetyltransferase 2
105	136	PC120740D  D	Ω	311380	HSTCP1 Human t-complex polypeptide I gene
106	137	PC010853D	₽	4506660	Homo sapiens ribosomal protein L7a (RPL7A) mRNA
107	139	PC030968D	۵	4507668	Homo sapiens tumor protein translationally-controlled 1 (TPTI) mRNA
	138	PC031146D   D	٥	8924228	NM 018636.1 Homo sapiens hypothetical protein PRO2987 (PRO2987)

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docoringion	professional	Ribosomal Proteins L2	in (PR00644)		<b>Oproteinikinas</b>	Protein kinase domain	nejreceptor <u>ass</u>	potassium AT	and stilbene s	ne-deaminase (	neogenin/(chic	Fibronectin type III domain	Immunoglobulin domain	Ribosomal protein L23	Keich iikeeg	otif	BTB/POZ domain	se family, p85-	bilorofrapopio	Inhibitor of Apoptosis domain	Caspase recruitment domain	ter, C3HC4 typ	Zinc finger, C4 type (two domains)	ein istas (RRIS)	nal protein L7A	Ribosomal L39 protein	Fibonucleoride	leotide reducta	MAKEDINHIW	Ubiquinone/pla	nuclearantige		Nysosomal-ass	ne-associated n	casein kinaset	Protein kinase domain	601411MAGE		<b>feukaryotictra</b>	anine nucleotid	<b>bZIP</b> transcription factor	Istaufen (Drosc	stranded RNA
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	a  0106060034	4506729	Down-regulated	H6mo sapienstribos	Homosapiensfribosomaliproteintss((R.P.S.s.))mRNAvantagens   Kalendara		起于温暖的	<b>17888</b>		
	PC030301D  D	4506729		Ribosomal S7	Ribosomal protein S7p/S5e	245.5	3.90E-71	51 204	4	
1	PC030326U  U	4507149		<b>Homoisapiens</b> isuper	Hemötsapiekistipetöxide-ut <del>smussapisolubia(smyotophisalatetalisclerosisti</del> kauit)/sodd <del>imrny</del> ki	बाद्मबाहिट ह्म	istik(adült)	r(Sodinim	RNA KELL	
-	PC030326U  U	4507149		soden	Copper/zinc superoxide dismutase (SOD 339.5	339.5	2.50E-105	1 154	4	
PC392 P	PC030425U U	415819		HSMK167-H.Sapiens	HSMK167-H.Sapiensimki6787mRN/AX(15ng/type)Itorganti.gen[61fm8n6ci0nallantibc34)IK: 2678-38	(fmonoclonal	<b>Fantibody</b> K			
<u>d.</u>	PC030425U U	415819		FHA	FHA domain	83.5	2.20E-22	16 27		
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<u>"</u>	PC030425U U	415819		Ribosomal S3 C	Ribosomal protein S3, C-terminal doma	2.5	7.30E-01	620 642	12	
<u>a.</u>	PC030425U  U	415819		HMG14 17	HMG14 and HMG17	-12.8	9.10E-01	981 901	9	
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<u> </u>	PC030471U U	31397		fn3	Fibronectin type III domain	1202.8	0.00E+00	2046	2123	
	PC030471U U	31397		lm]	Fibronectin type I domain		4.20E-250	2237 22	2272	
<u>-</u>	PC030471U U	31397		fn2	Fibronectin type II domain	194.4	1.60E-74	393 434	14	
	PC030471U U	31397		CXCXC	CXCXC repeat	5.7	6.30E-01		2264	
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PC033 P	PC030732U  U	4504375		Homogapiens/H.fac	HomosapiensH.factor/h:(complement).(HRII)ImRINARI			は時代記	SHOW SHOW THE SECOND	
ď	PC030732U  U	4504375		sushi	Sushi domain (SCR repeat)	1149.3	0.00E+00	1167 112	1228	
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<u>a.</u>	PC030931U U	337506		Ribosomal S24e	Ribosomal protein S24e	194	1.20E-55	23 105		
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	PC030968D   D	4207669		тстР	Translationally controlled tumor prot	375.5	2.80E-110	91	691	
4	PC030968D  D	4507669		MethyltransfD12	D12 class N6 adenine-specific DNA med 3.5	13.5	3.005-01	74 99		
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Ь	PC032046D   D	7657326								
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4	PC040156D  D	4505749		PFK	Phosphofructokinase	929.6		402		
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_	PC040158U U	4826950		trypsin	Trypsin	277	1.90E-88	30 245	15	
ď	PC040158U U	4826950		toxin 4	Anenome neurotoxin	-3.3	4.70E-01			
PC068 P	PC04041U U	4826880		H6mo(sapiens)oxid	H6majsapiensjoxidasej (cytochrome.c)jassemblyllelikej(@xexili9)mRyVAV   E. 1. 25.13.	MIDITERNA		8		
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	_	5174657		Ndr	Ndr family	716	~	24	366	
ŀ	PC040734D  D	5174657		abhydrolase	alpha/beta hydrolase fold	10.3	1.90E-03	89 30	309	

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	PC040972U	U 4885133		6ZIP	bZIP transcription factor	1.89	4.80E-19	2930	2962	
	PC040972U	U 4885133		W	M protein repeat	29.7	3.50E-06	2972	2992	
	PC040972U	U 4885133		KID repeat	KID repeat	26.6	3.10E-05	2938	2948	
	PC040972U	U 4885133		filament	Intermediate filament protein	13.2	8.80E-04	2810	2833	
	PC040972U	U 4885133		Trp repressor	Trp repressor protein	-16.9	5.50E-02	1065	1157	
	PC040972U	U 4885133		RNA pol L	RNA polymerases L / 13 to 16 kDa subul-28.7	-28.7	9.90E-02	840	923	
	PC040972U	U 4885133		Myosin tail	Myosin tail	4.3	1.40E-01	2283	2338	
	PC040972U	U 4885133		DUF164	Uncharacterized ACR, COG1579	1.16-	1.80E-01	2560	2797	
	PC040972U	U 4885133		HALZ	Homeobox associated leucine zipper	6	1.80E-01	2885	2928	
	PC040972U	U 4885133		OSCP	ATP synthase delta (OSCP) subunit	4.1	2.10E-01	2283	2294	
	PC040972U	U 4885133		K-box	K-bax region	40.4	3.10E-01	2440	2524	
	PC040972U U			HlyD	HlyD family secretion protein	-60.5	3.30E-01	2461	2730	
	PC040972U	U 4885133		DUF38	Domain of unknown function DUF38	3.9	4.00E-01	1888	1914	
	PC040972U	Ω		dynamin 2	Dynamin central region	-179.4	4.20E-01	991	1223	
	PC040972U	Ü		HRI	Hr1 repeat motif	4.4	4.70E-01	2201	2271	
	PC040972U	U 4885133		Apolipoprotein	Apolipoprotein A1/A4/E family	-118.2	4.90E-01	2295	2547	
	PC040972U	U 4885133		formyl transf	Formyl transferase	3	5.60E-01	3068	3081	
	PC040972U	U 4885133		ERM	Ezrin/radixin/moesin family	-227.4	6.50E-01	2028	2290	
	PC040972U	U 4885133		Tropomyosin	Tropomyosin	1.3	7.20E-01	2418	2451	
	PC040972U	U 4885133		Borrelia orfA	Borrelia ORF-A	-107.4	7.40E-01	417	744	
	PC040972U	U 4885133		PFEMP	Plasmodium falciparum erythrocyte men -89.6	-89.6	7.90E-01	2844	2950	
	PC040972U	U 4885133		BglG antitermin	Transcriptional antiterminator bglG f	4.4	8.40E-01	2891	2967	
	PC040972U	U 4885133		TFIIE beta	TFIIE beta subunit core domain	-15.1	8.40E-01	266	624	
	PC040972U	U 4885133		TarH	Tar ligand binding domain homologue	-28.4	8.80E-01	2666	2793	
	PC040972U	U 4885133		FliD	Flagellar hook-associated protein 2	-252.1	9.10E-01	2261		
PC057	PC041029U	U 4589596		REPORTED HIS COLOR OF THE PROPERTY OF THE PROP	ABQESIIGSIIHamaisspiensimRNAtionKIAA0978proteincampletecdsp.	oletecusion	to a market			
	PC041029U	U 4589596		Iaminin Nterm	Laminin N-terminal (Domain V1)	37	8.80E-14	20	295	
	PC041029U	U 4589596		laminin EGF	Laminin EGF-like (Domains III and V)	31.8	8.00E-07	297	341	
	PC041029U	U 4589596		EGF	EGF-like domain	3.9	5.20E-01	299		
PC194	PC041338U	U 8051621		oficial supides to more	Homossapiens 2,5120 iigoaden ylates ynthetasell ((OASII) transon plyatian il Bit Stri RNA)	napiliyariani	EI 8 THE NA			
	PC041338U	U 8051621		NTP transf 2	Nucleotidyltransferase domain	0.3	4.10E-02	53	142	
PC112	PC041980U	U 6735452		HSASAMOOMHOARSH	HSA99和09加HSmStapiens mRNANorB ind Ippotein(Beindubene) mental	Mene) Here		真然意		A September of the second
	PC041980U	Û								
<u>Ş</u>	PC042021D	D	Down-regulated	Homolsapiens/PPP	អ្នងការខានាក្រុកមានអ្នកមានអាក្សាក្រុកមានការប្រជាជាក្រុកបានជារប្រជាជាការបានការប្រជាជាការបានការបានការប្រការបានក្	printecall	(BREIBRI)	IMRNA P	At translated pro	ners
	PC042021D	D		SAM	SAM domain (Sterile alpha motif)	109.5	3.30E-30	11	774	
	PC042021D	D		integrase DNA	DNA binding domain of tn916 integrase 28.1	28.1	1.10E-05	187	251	
	PC042021D	D		WHEP-TRS	WHEP-TRS domain	15.9	1.20E-04	123	137	
	PC042021D	D		DUF16	Protein of unknown function DUF16	-22.2	1.40E-01	8	167	
	PC042021D	D 4505987		bZIP	bZIP transcription factor	5.2	3.20E-01	205	244	
	PC042021D	D		STAT	STAT protein, all-alpha domain	-71.8	5.40E-01		162	
PC088	PC050149U	Ú		AB0048849H5motse	ABOOA88AEHOmotsapiensfiiiRNAEforiPKO:alphaya.					
	PC050149U	U		pkinase	Protein kinase domain	245.9	2.90E-71	409	889	
	PC050149U	U [2217931		AZM	Alpha-2-macroglobulin family		2.40E-01	471	493	

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	263		2215	2085	2014		1882	897	1775	578	1177	974	397		1980	1290	1698	1299	1422	2118	1635			11	162	74	<b>(文)</b>			105		298	330		8		921	346	658	964	602	483	
Г	128	Village 1		2 2065	2 2005	2 1263	1 1850	1 864	1 1559	1 553	1 725	916 1	1 363		1 1963	1601	1366	1 1177	1 1248	1 2103	1 1576	1150	N.A. CONTRACT			1 53	(I) 和R	_		5 11			$\neg$		3 4			4	П			1 465	
	8.40E-01			9.30E-12	4.20E-02	8.80E-02	1.00E-01	1.20E-01	1.20E-0	1.50E-01	2.20E-01	3.90E-01	5.00E-01	5.10E-01	5.90E-0	6.30E-0	7.40E-01	7.80E-01	8.00E-01	8.20E-01	9.60E-01	9.70E-01	U2)mR	6.60E-02	1.80E-01	2.20E-01	A CIETUR		A)TERN	6.30E-55	beta	1.50E-88	1.90E-08		2.20E-33	1.60E-01	4.	8.10E-104 281	4.00E-01	6.20E-01	6.40E-01	7.70E-01	100
	27.44	DilVZaX4	77.2	48.2	14	1.7-	3.1	6.7	-89.1	3.4	-123	-9.6	-3.8	-21.2	9.1-	1.98-	+101-4	9'01-	-167.8	3.4	-6.3	-21.9	idepar dang	5.7	99-	4.2	neprotein		<b>р)</b> ((БКВР)	179.2	it catalytic	303.4	27.4		120.1	-62	(NATE)THIRNALS	354.1	45.7	-0.4	-72.9	1.5	HENNA
	Uncharacterized ACK, COCIS/9	NATO2000889.0Homolsapiensagojejaanioanijeenseojejijaabianijvaskase	GRIP domain	M protein repeat	Involucrin repeat	Ribosomal L29 protein	rase IV, subunit		OG1579	Tropomyosin	Adhesin lipoprotein	Uncharacterized BCR, COG1937	UvrB/uvrC motif	ATP synthase alpha/beta chain, C term	Isocitrate lyase family	CagE, TrbE, VirB family, component of	Borrelia ORF-A	SEA domain	aknown function DUF28	Bacterial DNA-binding protein	Major surface glycoprotein	Transposase	Homosapiens dyncincy topias michightifice mediatepotypeptide 21 (DNGU2) im RNA	Cell division protein	ABC transporter	SRP54-type protein, GTPase domain	NMI 00364 [F] [Homosapienslinterferoninducedinansmembraneprotein] (* (1614 M.) Krinn M. Krinn (* 1616 M.)		N.M. 1000 801 All Hombisa piens HAKS 06-binding protein II.A. (nie ko.) (na KB.P. IV.) ym R.V.A.	FKBP-type peptidyl-prolyl cis-trans ison 179.2	NM 1002/100 (Homolsapiens protein kinase) CAMP-dependent caralytic, leta	Protein kinase domain	Protein kinase C terminal domain	Hömölsapiensfribosomaliproteintiff Af(R Pijf 4) im RMA	Ribosomal protein L14	Ribosomal L27e protein family	Homosapiensineuronaraboptosiisiinhibitosyproteini(NAIP)m	Inhibitor of Apoptosis domain	ATPase family associated with various	Thermophilic metalloprotease (M29)	ABC transporter	NB-ARC domain	Homosapiensiserine protessetinhibit 62-Kazatitypetsi(SEINKs) jim Rin Au
	DUF 164 Stathmin	NWE00203821015	GRIP	Σ	Involucrin	Ribosomal L29	DNA topoisolV	bZIP	DUF164	Tropomyosin	Lipoprotein 7	DUF156	UVR	ATP-synt ab C	וכר	Cage TrbE VirB	Borrelia orfA	SEA	DUF28	Bac DNA binding	MSG	Transposase 8	Homosapiensidyne	GTP_CDC	ABC tran	SRP54	NWE00364 FIFTH OF		HOHI   1810 08 000 MIN	FKBP	NM TOO 2/1/2/IN THOU	pkinase	pkinase C	(Homosapiens) nbo	Ribosomal L14e	Ribosomal L27e	Homosapiensineur	BIR	AAA	Peptidase M29	ABC tran	NB-ARC	Homolsapiensiserin
																																					Down-regulated						
	221/931	6715600	6715600	6715600	6715600	6715600	6715600	6715600	6715600	6715600	6715600	6715600	6715600	0095129	6715600	6715600	0095129	6715600	0095129	6715600	6715600	6715600	5453634	5453634	5453634	5453634	4504581	4504581	4503725	4503725	4506057	4506057	4506057	4506601	4506601	4506601	4758752	4758752	4758752	4758752	4758752	4758752	5803219
	0 100	<u> </u>	10 01	10 01	10 0	10 01	10 01	10 01	10 01	10 U	וט ט	10 U	10 01	10 01	10 01	10 0	10 U	0 01	0 01	າດ ດ	n n:	10 01	6U U	eu Ju	6U U	6U U	on [n	00 N	30 0	30 00	00 00	00 N	00 [U	ות תו	וח ח	10 0	a lo	SD D	SD D		a ds	3D D	0 D
	PC050149U	PC0501511	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050151U	PC050296U	PC050296U	PC0502961	PC050296U	PC050620U	PC050620U	PC050853U	PC050853U	PC051210U	PC051210U	PC051210U	PC051231U	PC051231U	PC051231U	PC051745D	PC051745D	PC051745D	PC051745D	PC051745D	PC051745D  D	PC100   PC052029U
		PC087	1																				PC085				PC101		PC060		PC076			PC083			PC90						PC100

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1046	363	823			171	1631	8161	77	807	1318	1250	1817	425	1062	748	8681	608	1108	966	1684	1832	1548	1165	1220	1127	1077	1353	1534	1317		K	2768	1740	1082	1416	9681	· 8061	2352	1426	2413	8161	2736	1818
993		751	Γ		П	1073	8681	33 [7	3 282	1083	1018	1788	171	1 596	742	1863		1034	009				1062		П	╗					B	2724	П		1394	9281	1892	1779	1382	2401	1844	П	9991
3.70E-49	Г	6.50E-01	7.40E-01	<b>Sparifile</b>	0.00E+00	.20E-234	3.70E-20	2.40E-18	S.90E-04	6.60E-02	8.70E-02	8.80E-02	9.50E-02	1.20E-01	1.30E-01	1.80E-01	1.80E-01	2.10E-01	2.20E-01	2.70E-01		3.30E-01	4.00E-01	_		6.10E-01	7.30E-01			9.60E-01		4.50E-159			7.00E-03	3.10E-02	_	1.90E-01			7.40E-01		7.50E-01
172.5		_	-10.8	110) THEN	1495.3	788.7			22.3	9.86-	8 9'98-		-394.9	135.3				-0.6	414.1	-38.3	10.5		47.4			4.5	-36.2	-110.7	8		RNA	,				16.6		-263.9					-34.7
Kazal-type serine protease inhibitor   17	l		Hirudin -10	HUMINAKOHCB Human nonmuscie myösinheavyychän Blonnin 0) minnakamini jeds	Myosin head (motor domain)	Myosin tail 78	M protein repeat 76.1	Myosin N-terminal SH3-like domain 70.1	1Q calmodulin-binding motif [22]	Apolipoprotein A1/A4/E family -9	6	bZIP transcription factor 7.2		ion	Tub family 0.1	Tropomyosin 3.2	rotein		Hsp70 protein	ne efflux protein	Involucrin repeat 10	ain	KE2 family protein   4	HlyD family secretion protein -65	Nucleosome assembly protein (NAP) 2.5	UvrB/uvrC motif	5 protein	BAR domain -1	Transaldolase	Viral RNA dependent RNA polymerase [0.5]	NW 1004415. HH 3 more apiens (desmoplatin) (DRIP) DRIP (DSP) mRNA 1	Plectin repeat 53	bZIP transcription factor 23	Spectrin repeat 24	Myosin tail 9.3	M protein repeat	GGL domain 5.8	st complex subunit	pper	RNA polymerase beta subunit 0.2	Hr1 repeat motif -6.6	ymerase family B, exonuclease	Troponin -3
kazal	RNA POL M	DnaJ CXXCXGXG	Hirudin	наммионсв	myosin head	Myosin tail	Σ	Myosin N	ði	Apolipoprotein	DUF164	bZIP	Prismane	K-box	Tub	Tropomyosin	Lipoprotein 1	HRI	HSP70	OEP	Involucrin	kinesin	KE2	HIyD	NAP family	JUVR	Birna_VP5	BAR	Transaldolase	PV RdRp	Down-regulated NW 004415.14	Plectin_repeat	bZIP	spectrin	Myosin_tail	Ψ	G-gamma	Exo70	HALZ	RNA pol B	HRI	8	Troponin
5803219	5803219	5803219	5803219	641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	[641958	641958	641958	641958	641958	641958	641958	641958	641958	641958	4758200 Dow	4758200	4758200	4758200	4758200	4758200	4758200	4758200	4758200	4758200	4758200	4758200	4758200
PC052029U IU	PC052029U U	PC052029U U	PC052029U U	PC093 PC052095U U	PC052095U U	PC052095U U	PC052095U U	PC052095U  U	PC052095U U	PC052095U U	PC052095U U	PC052095U· U	PC052095U  U	PC052095U U	PC052095U U	PC052095U U	PC052095U U	PC052095U U	PC052095U  U	PC052095U U	PC052095U U	PC052095U U	PC052095U  U	PC052095U  U	PC052095U U	PC052095U  U	PC052095U U	PC052095U U	PC052095U  U	PC052095U  U	PC129   PC060144D   D	PC060144D D	PC060144D D	PC060144D D	PC060144D  D	PC060144D D	PC060144D D	PC060144D D	PC060144D D	PC060144D D	PC060144D D		PC060144D  D

Table 3

	PC060144D	D 4758200		dilsold	Phospholipase A2	3	7.70E-01	2553	2566	
	PC060144D	D 4758200		Transposase 12	Transposase	-162.5	7.80E-01	1412	1720	
	PC060144D	D 4758200		integrase DNA	g domain of tn916 integrase	-7.2	8.80E-01	259	328	
	PC060144D	D 4758200		filament	Intermediate filament protein	8.1	9.80E-01	1552	1582	
	PC060144D	D 4758200		Translin	'	-86.4	10-306.6	1283	1438	
PC132	PC060441U	U 1688258		HSUMBOAS Humanyo	#S@ag(4S)Human(co)lagenaseand strome(ysin/genes)(comple	eteleds yandı	netalloelast	ascigence	erercusyandimetalioelastaseigerieppärtialiousiinen	San San San San
	PC060441U	U [1688258		Peptidase M10	Matrixin	415.2	3.10E-122	37	204	
	PC060441U	U 1688258		hemopexin	Hemopexin	222.2	3.80E-64		466	
	PC060441U	U 1688258		Astacin	Astacin (Peptidase family M12A)	-101.3	1.60E-02	7	264	
	PC060441U	U 1688258		PG_binding_1	Putative peptidoglycan binding domain	-3.3	2.60E-02		16	
	PC060441U	U 1688258		UDPGP	UTP-glucose-1-phosphate uridylyltran	1.9	8.40E-01	248	266	
PC130	PC060443U	U 4506731		Mondosapiens/ribos	Homosapiensfrihosomaliproteinis 6f(RPS6)mRN/Arconteg		Too! STATE			
	PC060443U	U 4506731		Ribosomal S6e	Ribosomal protein S6e	312.2	3.30E-91	]	_	
PC124	PC060474U [1	U 4759322		#Hamolsapiens/wing	ilitamoisapiensiwinglesstypenMMTWintegrationkilitätamiliamembera Billyanita BilmRNA	nember/2BI((	WINTED B) FILE	-		
	PC060474U	U 4759322		wnt	wnt family	656.5	1.00E-239 S2		361	
	PC060474U	U 4759322		Keratin B2	Keratin, high sulfur B2 protein	-87.2	8.50E-01		364	
PCI 52	PC060529U	U 4503821		M-cmo, sapiens (Fr.)	National sapiens Hava Leinding protein (HYB 1120160) (HAYB) Im Ray Ryand	Revisiyand (tra	(rranslated/products)		如底 到 在 国	Color of Constant Color
	PC060529U	U 4503821		SH3	SH3 domain	<i>L</i> -	3.10E-02	514	570	
	PC060529U	U 4503821		vATP-synt E	ATP synthase (E/31 kDa) subunit	-104.2	9.80E-01	464		
PC197	_	D 4557257	Down-regulated		(Homosapienstadenylaicicyclasess)(brain) ((Alocayas)) mRNA					
		D 4557257		guanylate cyc	Adenylate and Guanylate cyclase catal	632	1.80E-187	973	1172	
	PC060743D	D 4557257		Bac export 3	Bacterial export proteins, family 3	-39.6	3.80E-01	2	347	
		D 4557257		GARS	ylglycinamide synthetase,	-92.8	5.50E-01		320	
		D 4557257		prion	Prion protein	-98.1	7.50E-01		268	
		D 4557257		Тґкн	Sodium transport protein	-223.6	9.40E-01	42		
PC193	PC060793D	D 4507583	Down-regulated		NMR00004391/IHomolsapiensituinotinecrosis, factor receptorisuperfamily.	uperfamily	LACTOR SE	是是就	爾	ENTER CONTRACTOR
	PC060793D			TNFR c6	TNFR/NGFR cysteine-rich region	94.9	8.30E-26	129	165	
	PC060793D  D	D 4507583		death	Death domain	70.7	1.60E-18	231		
PC199	PC060940U	U 5052075		H6m8IsapiensIPAPS	Hömörsapiensi Parsayni hetase 20 (PAPSS2) mayar and an analysis		THE PROPERTY OF	相邻的		
	PC060940U	U 5052075		ATP-sulfurylase	ATP-sulfurylase	683.7	4.70E-203	284	612	
	PC060940U	U 5052075		APS kinase	Adenylylsulfate kinase	395.1	3.60E-116	41	199	
	PC060940U	U 5052075		Thymidylate kin	Thymidylate kinase	-70	2.30E-01		207	
	PC060940U	U 5052075		6PF2K	6-phosphofructo-2-kinase	-123.6	3.20E-01		223	
	PC060940U	U 5052075		PRK	Phosphoribulokinase / Uridine kinase	3.1	3.90E-01		8	
PC188	PC061342D	D 386831	Down-regulated	H@MINITED HUMBY	HOM Ning Humanii eukocyte achesion protein pils 09 stabhasubuni i genete konsti 64 teish	<b>Subunifigen</b>	elexonsti 6	囊		
	PC061342D	D 386831		vwa	von Willebrand factor type A domain	239.3	2.80E-69		329	
	PC061342D	18898E Q		FG-GAP	FG-GAP repeat	200.6	1.30E-57	581	633	
	_	D 386831		integrin_A	Integrin alpha cytoplasmic region	30.6	1.90E-06	٦	1143	
	$\overline{}$	D 386831		Polyoma coat2	Polyomavirus coat protein	1.3	6.10E-01	522	-	
PC184	PC061477U	U 4506387		IH 6 molsapiens IRAD	KAID 28 ((SPECIEVISIAE) In Omologi BI (RAKID 28 B) Im RNA 12.	<b>III RANAMA</b>		の対対		
	PC061477U	U 4506387		ubiquitin	Ubiquilin family	105.2	3.20E-29	_	78	
	PC061477U	U 4506387		UBA	UBA/TS-N domain	71.5	9.40E-19		404	
	PC061477U	U 4506387		integrin B	Integrins, beta chain	6.2	4.10E-03	364		
PC213	PC061528D	D 4506701	Down-regulated	"Homoisapiensiribos	(Pitomoisapiensiri bösömälipiroiteini S229 (RRS28) imitavi Access (I consequenti Consequenti (I consequenti Co					

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142	<b>DF2WS</b> i	464	630	94	20	299	<b>高額税</b>	521	135	250	386	( Table 1	498	医水型	74	147	156	Z) 計R	84		123		188	95		328	112	84	1991	464	630	91	20	299			No.	213	357		901	<u>8</u>	
1	CludesIM	34	889	56	2	594	A SECOND	270	75	228	261		459	2000	_	<u> </u>	103	in)(SRR	4	REMESSO.	21		104	47		161	6	54		34	665	26	2	594			THRIVE	42	205		39	55	
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PC090677D         D         397218         WDd domain, G-beta repeat         200.3         1.60E-57         275         311         Excession           PC090672D         D         7670448         Down-regulated         WDd domain, G-beta repeat         200.3         1.60E-57         275         311         Excession           PC090754U         U         4503473         GTP EFTU         GIPP EFTU D3         Elongation factor Tu C-terminal domai         201.1         8.80E-58         269         378           PC090754U         U         4503473         GTP EFTU D3         Elongation factor Tu Green and domain         201.1         8.80E-58         269         378           PC090754U         U         4503473         GTP EFTU D3         Elongation factor Tu Gomain         201.1         8.80E-58         269         378           PC09078BD         D         5031639         GTP EFTU D2         Elongation factor Tu domain         201.1         8.80E-58         269         378           PC09078BD         D         5031639         Down-regulated         BGmcgapiensjeric(GNII)YmRNAScapensies and processes         BGC-27         17.0E-86         169         373           PC09078BD         D         5031639         Down-regulated         BGGmcgapiensjeric(GNIII)YmRNAscapens	PC310	PC090677D	<u>ا</u>	307218	own-regulated	ниммнвиизяни	mani MHGproteinihomologoustotchicken	Boomplex	proteinImR	Arcomp		
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PC090754U   U 4503473   GTP EFTU   Elongation factor Tu GTP binding doma   237.8   8.20E-65   4   175     PC090754U   U 4503473   GTP EFTU D3   Elongation factor Tu C-terminal domai   201.1   8.80E-58   269   378     PC090754U   U 4503473   GTP EFTU D3   Elongation factor Tu C-terminal domai   201.1   8.80E-58   269   378     PC090754D   U 4503473   Down-regulated   Elongation factor Tu domain Z   1.50E-27   187   265     PC090788D   D 5031639   Down-regulated   Elongation factor Tu domain Z   201.1   8.80E-27   1.20E-27   1.20E-27     PC090842U   U 4557032   Elongation factor Tu domain Z   201.1   201.2     PC090842U   U 4557032   Elongation factor Tu domain Z   201.1   201.2     PC090842U   U 4557032   Elongation factor Tu domain Z   201.1   201.2     PC091028U   U 4557032   Elongation factor Tu domain Z   201.1     PC091028U   U 7662426   Elaminin Nterm   Laminin EGF   Laminin EGF	PC230	PC090754U	Ω	4503473		Homojsapiens(eukai	<b>Jone translation elongation factora la ph</b> a	NEIKENWO	EEUWIUN	MRNA		
PC090754U U 4503473   GTP EFTU D3   Elongation factor Tu C-terminal domai 201.1   8.80E-58   269   378   PC090754U U 4503473   GTP EFTU D2   Elongation factor Tu domain 2   98.6   1.50E-27   187   263   1.50E-28   1.50E-27   1.50		PC090754U	U	4503473		GTP EFTU	Elongation factor Tu GTP binding doma	237.8	8.20E-69	4	175	
PC090754U         U         4503473         GTP EFTU D2         Elongation factor Tu domain 2         98.6         1.50E-27         187         26.3           PC09078BD         5031639         Down-regulated (H6m703mptens)Gemitchforfalte/(GHN1th/mRA/NEMBER) (H2m203c) (H2m203c) (H2m203c)         BJOTTO (H2m203c) (H2m2		PC090754U	U	4503473		GTP EFTU D3	Elongation factor Tu C-terminal domai	201.1	Т		378	
PC090788D   Down-regulated     PEGNOTOSE   PEGNOTOSE		PC090754U	U	4503473		GTP EFTU D2	Elongation factor Tu domain 2	98.6	1.50E-27	187		
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PC090842U U 4557032   BJ6m06sapiens1actale delydrogenase, alpha/berla 197   1.20E-86   164   313     PC090842U U 4557032   Idh C   Jactate/malate delydrogenase, alpha/berla 197   1.20E-86   164   313     PC091028U U 7662426   Idhmini Nierm   Laminin Nierm   Laminin Nierm   Laminin Nierm   Laminin Nierm   Laminin Hormal (Domain VI)   31.8   8.00E-07   297   341     PC091028U U 7662426   EGF   Laminin EGF   Laminin Hormal (Domain VI)   31.8   8.00E-07   297   341     PC091028U U 7662426   EGF   EGF   EGF   EGF-like (Domain VI)   31.8   8.00E-07   297   341     PC091028U U 7662426   EGF   EGF   EGF   EGF-like domain   3.9   5.20E-01   299   326     PC091028U U 4732026   Peptidase M2   Angiotensin-converting enzyme   3415   0.00E+00   634   1228     PC091425U U 4732026   PupifyHypC family   -34   5.00E-01   1231   1286		PC090788D	D	5031639					Name of the last o			
PC090842U U 4557032   Idh C   Jactate/malate dehydrogenase, alpha/beta/297   1.20E-86   164   333     PC090843U U 4557032   Idh   Jactate/malate dehydrogenase, NAD bind 284.4   7.30E-87   1.20E-86   164   333     PC091028U U 7662426   Haminin Nterm   Laminin N-terminal (Domain VI)   37   8.80E-14   97   245     PC091028U U 7662426   Jaminin Nterm   Laminin EGF-like (Domain III and V)   3.7   8.80E-14   97   341     PC091028U U 7662426   EGF   EGF   EGF   EGF-like (Domain III and V)   3.18   8.00E-07   297   341     PC091028U U 7662426   Kyjill@is.69jif@mnisspiecens.converting enzyme   3.9   5.20E-01   299   336     PC091028U U 4732026   Kyjill@is.69jif@mnisspiecens.converting enzyme   3415   0.00E+00   634   1228     PC091425U U 4732026   HupF HypC   HupF/HypC family   3415   1286     PC091425U U 4732026   HupF HypC   HupF/HypC family   3415   1286     PC091425U U 4732026   HupF HypC   HupF/HypC family   3415   1286     PC091425U U 4732026   HupF HypC family   134   1286     PC091425U U 4732026   HupF HypC family   134   1351   1286     PC091425U U 4732026   HupF HypC family   134   1351   1286     PC091425U U 4732026   HupF HypC family   134   1351   1286     PC091425U U 4732026   HupF HypC family   134   1351   1286     PC091425U U 4732026   HupF HypC family   134   1351   1286     PC091425U U 4732026   HupF HypC family   134   134   1351   1286     PC091425U U 4732026   HupF HypC family   134   134   134   1351   1286     PC091425U U 4732026   HupF HypC family   134   134   134   1351	PC233	PC090842U	ח	4557032		Momo(sapiens))actal	ie dehydrogenase BY (UDHB) im RN will an		Jan. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.	2		
PC090842U U   4557032   Idh   Iactate/malate dehydrogenase, NAD bind 284.4   7.30E-83   19   162   1		PC090842U	U	4557032		Idh C	lactate/malate dehydrogenase, alpha/beta	297	Ħ	T	333	
PC091028U U 7662426   HtomograpiersychyAooy76/profeiri/(Rt/Aooy76/profeiri/Rt/Aooy76/pr		PC090842U	Ω	4557032		ldh	lactate/malate dehydrogenase, NAD bind	284.4		<u></u>		
PC091028U         U         7662426         laminin Nterm         Laminin M-terminal (Domain VI)         37         8.80E-14         50         295           PC091028U         U         7662426         laminin EGF         Laminin EGF-like (Domains III and V)         31.8         8.00E-07         297         341           PC091028U         U         7662426         EGF         EGF-like domain         5.00E-01         297         341           PC091425U         U         4732026         Walill@85QHGm0sspie/sfrighedenis/lichidenteringenzyme         3415         0.00E-06         654         1228           PC091425U         U         4732026         Peptidase M2         Angiotensin-converting enzyme         3415         0.00E-06         654         1228           HupF HypC         HupF/HypC family         -34         5.00E-01         1231         1286	PC236	PC091028U	D	7662426		1Homo[sapiens]KI/A	40976 protein (KIAA0916) mRNAETED				_	
PC091028U         U         7662426         laminin EGF         Laminin EGF-like (Domains III and V)         31.8         8.00E-07         297         341           PC091028U         U         7662426         EGF         EGF-like domain         3.9         5.20E-01         299         326           PC091425U         U         4712026         WEBIRGS GOBIEST GORDING STREET		PC091028U	Ω	7662426		laminin Nterm		37	7		295	
PC091028U         U         7662426         EGF         EGF-like domain         3.9         5.20E-01         299         326           PC091425U         U         4712026         Whitescopies in graph of the properties in gr	L	PC091028U	Ω	7662426		laminin EGF		31.8	П		741	
PC091425U         U         4712026         Winifigs.6Sgliff@mösspielers*ärrgiöfer		PC091028U	n	7662426		EGF	EGF-like domain	3.9				
U         4732026         Peptidase         M2         Angiotensin-converting enzyme         3415         0.00E+00         634           U         4732026         HupF HypC         HupF/HypC family         -34         5.00E-01         1231	PC324		n	4732026		Whiliss 69 Hibmolsa	piens angiötensin/Il cohvertingtenzymelpre	curson				
U   4732026   HupF HypC   HupF/HypC family   -34   5.00E-01   [1231		PC091425U		4732026		Peptidase M2	Angiotensin-converting enzyme	3415	_	٦	1228	
		PC091425U	n	4732026		HupF HypC	HupF/HypC family	-34			1286	

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9	44 201/00	400000	159	127			5	333	251	6	6	ilisoforn		423	67	230		457	246	431	8	354	289	122				873	552			õ	500	Snc h1252	112	_	32	126	-1				
7 70F-01	The Park	HKINAR	2.80E-93	9.10E-01	mplete cds	<b>聚等的</b>	3.00E-111	3.00E-61	3.80E-28	6.10E-01	9.80E-01	exfelphalsubuni	2.80E-164 138	1.40E-39	2.80E-20	9.90E-01	<b>医医院验验 各种的</b>	1.80E-134 457	2.00E-02	2.30E-01	2.70E-01	4.70E-01	4.90E-01	7.90E-01	8.20E-01	医学艺	1.40E-117	2.90E-01	3.90E-01	6.10E-01	me gene	1.90E-88	4.70E-01	phómarch	6.80E-101	5.80E-61	6.50E-01	7.50E-01	9.80E-01		4.00E-70		
0.0	100	MAREK	319	-51.4	<b>FINRNATCO</b>	hawana		212.7		-99.3	138.3	Complexia				97.9	ন্দ্রানাতা হ	455.9	4.8	-16.7			-6.9	-20.8	-11.8	NA数数	399.8	-2.9	-257.7	-23.5	trypticienz	277	-3.3	dekinisilym	344.3	211.7	-201.8	-101.5	-29.6	((cox+))	242.1	dellering	
Marhudand Co Lynniach	INCIDITIONAL PROPERTY OF THE P	1990ciated p	metallopeptidase family M24	PBP/GOBP family	APPOROVABIH omorsapienslubiquitin associated proteini (NAG20) im RNAI complete cus	XXX88691/HSEFIIIA/GHuman, mr NAVior elongation incorn salpha XXIIIIA MANAINI MANAINI MANAINI MANAINI MANAINI M	Elongation factor Tu GTP binding doma 378.7	Elongation factor Tu C-terminal domai 2	Elongation factor Tu domain 2	oxidor	Conserved hypothetical ATP binding pr [-138.3	Homorsapiens/Attrasynthase/H-Firansporting/Initochondrial/Fileompl	ATP synthase alpha/beta family, nucleo 554.9	ATP synthase alpha/beta chain, C termi 1140.6	ATP synthase alpha/beta family, beta-b	Tungsten formylmethanofuran dehydrog -97.9	NNMO 18300R H15m3/sapiens hypothetical protein Febril 01sf (FEB/14015).	Zinc finger, C2H2 type	BED zinc finger	LIM domain	in	MIZ zinc finger	ctor S-II (TFIIS)	PHD-finger	ANI-like Zinc finger	(Hömöjsapjensja Heprolöcadhenni(břáin hear), (9999DHn) mRNA開展期間	Cadherin domain	Adenovirus E3 region protein CR2	Alphaherpesvirus glycoprotein E	Cellulose binding domain	AEIX698019/alti/66330/Homorsapiens/stratum-comeum/chymotrypiic/enzyme/genera	Trypsin	Anenome neurotoxin	HSWANING Homorsapiens mRNAthom, HIV-associated non-Hodgkin shymphoma (Cloncini2:22) Kanas	NADH-Ubiquinone/plastoquinone (com/344.3	NADH-ubiquinone oxidoreductase chain 211.7	Sugar (and other) transporter	Cytochrome C biogenesis protein trans	Integral membrane protein DUF6	NMICONSCIPLINATION sapiens cytochrome croxidas etcubunianal (Goxe)	Cytochrome c oxidase subunit IV	M691.99MIHUMG0S2AtHumantG0S2Iproteinigenercompleteicdsing and	
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D	35038		ku	KU domain	570	7.70E-169	1 467	,	
PC101863U U	35038		filament	Intermediate filament protein	2.8	5.40E-01	559 568	no	
PC110249D D	4759258	Down-regulated	HomorsapiensPAC-11	Homorsapiens RAC-11 keifransposable Pelement (Wishing) min NNAM   SECT.		FH			2
PC110249D D	4759258		Zf-BED	BED zinc finger			23 72	_	
PC110541D D	5031779	Down-regulated	Homo Sapiens linier	Horno Sapiens finie free on gamma inducio i aprofeinu of (unido) im RN/ACT 200			<b>解系列 即</b>		
PC110541D D	5031779		NIH	HIN-200/IF120x domain	887.5	2.00E-264	518 685	S	
PC110541D D	5031779		PAAD DAPIN	PAAD/DAPIN/Pyrin domain	155.2	5.90E-44	3 88		
PC110541D D	5031779		lipocalin	d bind	8.8	1.20E-02	589 669	s T	
PC110541D D	5031779		pp-binding	Phosphopantetheine attachment site	3.9	1.00E+00			
PC110927U U	7020307		7020306ldbjjAK000	7020306 db  AKQ00303R   RKG00000B  HG000555p EnstG0 NANGO00020165KC OnBH ER06648KL	120302FFS4	CISHENDE			
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PC110940D D	4758950	Down-regulated	NATIO0009A2NINHSH	NMT00094944AHTHGmosspienspeptidyJpmiyAtsomenseJBI(Cyclophilin)B)V	lophilin(B)	<b>多种性。"</b> "	題		
PC1 10940D D	4758950		pro isomerase	Cyclophilin type peptidyl-prolyl cis-tr	395.4	3.00E-116	45 206	٦	
PC111168U U	4759284		NWGOOTHBIBLE	NMCOOMISHSHIP DENOISE piens obiqui in rearbox, il remina les reasolules	元司帅				
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PC111181U U	7416941		Tim17	Mitochondrial import inner membrane t  -59.6	-59.6	6.10E-02	59 210	0	
PC111181U U	7416941		Synapsin	Synapsin, N-terminal domain	7	1.90E-01	96 98		
PC111588D D	4503413	Down-regulated	Hömörsapiensidiphil	<u>ເຈົ້າວ່າ ເຈົ້າວ່າ ເປັນທີ່ ທີ່ທີ່ທີ່ທີ່ທີ່ທີ່ທີ່ທີ່ທີ່ ທີ່ ທີ່ </u>	enBligrowth	Mactor like	growth fac	or)K(D/IDR)TH	RNA - Assessment Section (1997)
PC111588D D	4503413		EGF	EGF-like domain	31	1.40E-06	108 143	3	
PC111669D   D	7705823	Down-regulated	NM#0.1610091/HGP	NM*01.610091/H6m68saptensingterminalisterpirensisterassecomplexamitatudus estilioopminalist	nplexvardilsi	bunit (100G	S-11126)TmR	NAC CONTRACT	
PC111669D D	7705823	_	Acetyltransf	Acetyltransferase (GNAT) family	70.4	1.90E-18	45 129	6	
PC120136U U	7706729		Homosapiens Jil 8%	HomoisaniensijijBixofiisoprofeint(ijiBixofiiso)imRiNA			9		
PC120136U U	7706729		T-box	T-box	380.6	8.10E-112 240		9	
PC120331U IU	4504425		NWGOOPHE SUITHER	NWGODIPSUIIHTEMSSEDIERSINIPHEMODIIIIWENOODI(Indinisioneelinomosomalyiproteiniik-1442)	elchromosor	nalyprotein			
PC120331U  U	4504425		HMG box	HMG (high mobility groap) box	161	1.50E-56		3	
PC120740D D	36796	Down-regulated	HSJI(GR)[HUman(re	HSJI(GRIJI) Umanitecomplex polypeptide il Vgenera and an extension			X		
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PC120740D   D	36796		ATP-synt B	ATP synthase B/B' CF(0)	4	3.60E-01	_		
PC120741D   D	5174389	Down-regulated	HORINITE SECTION OF THE PROPERTY OF THE PROPER	NME00589/HITHS morsapiens acety! Goenzymezavacety/transferase 22	ensept				
PC120741D D	5174389		thiolase	Thiolase, N-terminal domain	419.2	1.90E-123	1 268	8	
PC120741D   D	5174389		thiolase C	Thiolase, C-terminal domain	250.2	╗	272 396	9	
PC120741D D	5174389		ketoacyl-synt	Beta-ketoacyl synthase, N-terminal do	-118	3.40E-01	5 154	4	
PC121671U U	7661636		Homosapiens IDKR	Homosapiensjip Krz Ps 64 O 2082 birone ii ii O Krz Ps 64 O 2082) min Na Krz Ma	TI BYANE				
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# SEQUENCE LISTING

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Cys Gly Thr Pro Lys Gly Asn Arg Pro Val Ile Leu Thr Tyr His Asp 50 60

Ile Gly Met Asn His Lys Thr Cys Tyr Asn Pro Leu Phe Asn Tyr Glu 65 70 75 80

Asp Met Gln Glu Ile Thr Gln His Phe Ala Val Cys His Val Asp Ala 95 90 95

Pro Gly Gln Gln Asp Gly Ala Ala Ser Phe Pro Ala Gly Tyr Met Tyr 100 105 110

Pro Ser Met Asp Gln Leu Ala Glu Met Leu Pro Gly Val Leu Gln Gln 115 120 125

Phe Gly Leu Lys Ser Ile Ile Gly Met Gly Thr Gly Ala Gly Ala Tyr 130 140

Thr Leu Thr Arg Phe Ala Leu Asn Asn Pro Glu Met Val Glu Gly Leu 145 150 155 160

Val Leu Ile Asn Val Asn Pro Cys Ala Glu Gly Trp Met Asp Trp Ala 165 170 175

Ala Ser Lys Ile Ser Gly Trp Thr Gln Ala Leu Pro Asp Met Val Val 180  $$185\$ 

Ser His Leu Phe Gly Lys Glu Glu Met Gln Ser Asn Val Glu Val Val 195 200 205

His Thr Tyr Arg Gln His Ile Val Asn Asp Met Asn Pro Gly Asn Leu 210 215 220

His Leu Phe Ile Asn Ala Tyr Asn Ser Arg Arg Asp Leu Glu Ile Glu 225 230 235 240

Arg Pro Met Pro Gly Thr His Thr Val Thr Leu Gln Cys Pro Ala Leu 245 250 255

Leu Val Val Gly Asp Ser Ser Pro Ala Val Asp Ala Val Val Glu Cys 260 265 270

As Ser Lys Leu Asp Pro Thr Lys Thr Thr Leu Leu Lys Met Ala Asp 275 280 285

Cys Gly Gly Leu Pro Gln Ile Ser Gln Pro Ala Lys Leu Ala Glu Ala 290 295 300

Phe Lys Tyr Phe Val Gln Gly Met Gly Tyr Met Pro Ser Ala Ser Met 305 310 315 320

Thr Arg Leu Met Arg Ser Arg Thr Ala Ser Gly Ser Ser Val Thr Ser 325 330 335

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PRT

Homo sapiens

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Phe Phe Val His Glu Gly Tyr Gln Gly Leu Val Asp Gly Gly Asp His 50  $\phantom{-}$ 

Ile Lys Glu Ala Thr Trp Glu Ser Val Ser Met Met Leu Gln Leu Gly 65 70 75 80

Gly Thr Val IIe Gly Ser Ala Arg Cys Lys Asp Phe Arg Glu Arg Glu 85 90 95

Gly Arg Leu Arg Ala Ala Tyr Asn Leu Val Lys Arg Gly Ile Thr Asn 100 105 110

Leu Cys Val Ile Gly Gly Asp Gly Ser Leu Thr Gly Ala Asp Thr Phe 115 120 125

Arg Ser Glu Trp Ser Asp Leu Leu Ser Asp Leu Gln Lys Ala Gly Lys 130 135 140

Ile Thr Asp. Glu Glu Ala Thr Lys Ser Ser Tyr Leu Asn Ile Val Gly 145 150 150

Leu Val Gly Ser Ile Asp Asn Asp Phe Cys Gly Thr Asp Met Thr Ile 165 170 175

Gly Thr Asp Ser Ala Leu His Arg Ile Met Glu Ile Val Asp Ala Ile 180  $$185\$ Thr Thr Thr Ala Gln Ser His Gln Arg Thr Phe Val Leu Glu Val Met 195  $\phantom{\bigg|}200\phantom{\bigg|}$ Gly Arg His Cys Gly Tyr Leu Ala Leu Val Thr Ser Leu Ser Cys Gly 210 215 220 Ala Asp Trp Val Phe Ile Pro Glu Cys Pro Pro Asp Asp Asp Trp Glu 225 230 235 240 Glu His Leu Cys Arg Arg Leu Ser Glu Thr Arg Thr Arg Gly Ser Arg 245 250 250 255Leu Asn Ile Ile Ile Val Ala Glu Gly Ala Ile Asp Lys Asn Gly Lys  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$ Pro Ile Thr Ser Glu Asp Ile Lys Asn Leu Val Val Lys Arg Leu Gly 275 280 285Pro Ser Ala Phe Asp Arg Ile Leu Gly Ser Arg Met Gly Val Glu Ala 305 310 315 320 Val Met Ala Leu Leu Glu Gly Thr Pro Asp Thr Pro Ala Cys Val Val 325  $\phantom{\bigg|}330\phantom{\bigg|}$  335 Ser Leu Ser Gly Asn Gln Ala Val Arg Leu Pro Leu Met Glu Cys Val Gln Val Thr Lys Asp Val Thr Lys Ala Met Asp Glu Lys Lys Phe Asp 355 360 365Glu Ala Leu Lys Leu Arg Gly Arg Ser Phe Met Asn Asn Trp Glu Val 370 375 380Tyr Lys Leu Leu Ala His Val Arg Pro Pro Val Ser Lys Ser Gly Ser 385 390 395 400 His Thr Val Ala Val Met Asn Val Gly Ala Pro Ala Ala Gly Met Asn 405  $\phantom{\bigg|}410\phantom{\bigg|}410\phantom{\bigg|}$ Ala Ala Val Arg Ser Thr Val Arg Ile Gly Leu Ile Gln Gly Asn Arg  $420 \hspace{1.5cm} 425 \hspace{1.5cm} 430$ Val Leu Val Val His Asp Gly Phe Glu Gly Leu Ala Lys Gly Gln Ile 435 440 445Glu Glu Ala Gly Trp Ser Tyr Val Gly Gly Trp Thr Gly Gln Gly Gly 450 455 460Ser Lys Leu Gly Thr Lys Arg Thr Leu Pro Lys Lys Ser Phe Glu Gln 465 470 475 480 Ile Ser Ala Asn Ile Thr Lys Phe Asn Ile Gln Gly Leu Val Ile Ile

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485 490 495

Gly Gly Phe Glu Ala Tyr Thr Gly Gly Leu Glu Leu Met Glu Gly Arg 500 505 510

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Cys Gly Tyr Leu Ala Thr Met Ala Gly Leu Ala Ala Gly Ala Asp Ala 580 585 590

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Phe Asn Leu Tyr Ser Glu Glu Gly Lys Gly Ile Phe Asp Ser Arg Lys 645 650 655

Asn Val Leu Gly His Met Gln Gln Gly Gly Ser Pro Thr Pro Phe Asp 660 665 670

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Pro Asp Ser Gly Cys Val Leu Gly Met Arg Lys Arg Ala Leu Val Phe 705  $\phantom{\bigg|}710\phantom{\bigg|}710\phantom{\bigg|}720\phantom{\bigg|}715\phantom{\bigg|}$ 

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Cys Phe Cys Cys Ser Leu Ile Leu Phe Gly Ala Gly Leu Thr Arg Leu 100 105 110

Pro Ile Glu Asp His Lys Arg Phe His Pro Asp Cys Gly Phe Leu Leu 115 120 125

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Glu Phe Leu Arg Ser Lys Lys Ser Ser Glu Glu Ile Thr Gln Tyr Ile 225 230 235 240

Gln Ser Tyr Lys Gly Phe Val Asp Ile Thr Gly Glu His Phe Val Asn 245 250 255

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Arg Cys Phe Pro Asn Cys Pro Phe Leu Gln Asn Met Lys Ser Ser Ala 340 345 350

Glu Val Thr Pro Asp Leu Gln Ser Arg Gly Glu Leu Cys Glu Leu Leu 355 360 365

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Ile Val Pro Glu Met Ala Gln Gly Glu Ala Gln Trp Phe Gln Glu Ala 385 390 395 400

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Leu Leu Gly Cys Asp Leu Ser Ile Ala Ser Lys His Ile Ser Lys Pro 435 440 445

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Cys Ile Leu Arg Lys Leu Phe Ser His Asn Met Thr Arg Leu Arg Lys 610 620

Phe Met Val Tyr Phe Gly Lys Asn Gln Ser Leu Gln Lys Ile Gln Lys 625 630 635 640

Thr Pro Leu Phe Val Ala Ala Ile Cys Ala His Trp Phe Gln Tyr Pro 645 650 655

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Val Ser Ser Cys Gly Glu Leu Ala Leu Lys Gly Phe Phe Ser Cys Cys 690 695 700

Phe Glu Phe Asn Asp Asp Asp Leu Ala Glu Ala Gly Val Asp Glu Asp 705 710 715 720

Glu Asp Leu Thr Met Cys Leu Met Ser Lys Phe Thr Ala Gln Arg Leu 725 730 735

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His Gln Pro Glu Ile Ser Leu Gln Met Gln Leu Leu Arg Gly Leu Trp 835 840 845

Gln Ile Cys Pro Gln Ala Tyr Phe Ser Met Val Ser Glu His Leu Leu 850 855 860

Val Leu Ala Leu Lys Thr Ala Tyr Gln Ser Asn Thr Val Ala Ala Cys 865 870 875 880

Ser Pro Phe Val Leu Gln Phe Leu Gln Gly Arg Thr Leu Thr Leu Gly 885 890 895

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Ala His Phe Ser Val Leu Glu Thr Cys Phe Asp Lys Ser Gln Val Pro 930 935 940

Thr Ile Asp Gln Asp Tyr Ala Ser Ala Phe Glu Pro Met Asn Glu Trp 945 950 955 960

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Met Thr Met Leu Val Ser Cys Lys Leu Thr Glu Ile Lys Phe 1175 1180 1185

Ser Asp Ser Phe Phe Gln Ala Val Pro Phe Val Ala Ser Leu Pro 1190 1195 1200

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Pro Asp Glu Glu Thr Ser Glu Lys Phe Ala Tyr Ile Leu Gly Ser 1220 1225 1230

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1235 1240 1245

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Cys Leu Arg Val Leu Ser Phe Phe Lys Thr Leu Asn Asp Asp Ser 1265 1270 1275

Val Val Glu Ile Ala Lys Val Ala Ile Ser Gly Gly Phe Gln Lys 1280 1285 1290

Leu Glu Asn Leu Lys Leu Ser Ile Asn His Lys Ile Thr Glu Glu 1295  $\phantom{\bigg|}$  1300  $\phantom{\bigg|}$  1305  $\phantom{\bigg|}$ 

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Gln Glu Leu Asp Ile Ser Arg His Phe Thr Glu Cys Ile Lys Ala 1325 1330 1335

Gln Ala Thr Thr Val Lys Ser Leu Ser Gln Cys Val Leu Arg Leu 1340 1350

Asp Asp Ile Ala Leu Leu Asn Val Met Lys Glu Arg His Pro Gln 1370 1380

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Pro Ile Ile Gln Lys 1400

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Phe Asp Cys Gln Ser Pro Thr Ser Pro Phe Met Gly Ser Leu Arg Ala 35 40 45

Leu His Leu Val Glu Asp Leu Arg Gly Leu Leu Glu Met Met Glu Thr 50  $\,$  55  $\,$  60  $\,$ 

Asp Glu Lys Glu Gly Leu Arg Cys Gln Ile Pro Asp Ser Thr Ala Glu 65 70 75 80

Thr Leu Val Glu Trp Leu Gln Ser Gln Met Thr Asn Gly His Leu Pro 85 90 95

Gly Asn Gly Asp Val Tyr Gln Glu Arg Leu Ala Arg Leu Glu Asn Asp

105

Lys Glu Ser Leu Val Leu Gln Val Ser Val Leu Thr Asp Gln Val Glu 115 120 125

Ala Gln Gly Glu Lys Ile Arg Asp Leu Glu Phe Cys Leu Glu Glu His 130 135 140

Arg Glu Lys Leu Asn Ala Thr Glu Glu Met Leu Gln Gln Glu Leu Leu 145 150 155 160

Ser Arg Thr Ser Leu Glu Thr Gln Lys Leu Asp Leu Met Ala Glu Ile 165 170 175

Ser Asn Leu Lys Leu Lys Leu Thr Ala Val Glu Lys Asp Arg Leu Asp 180 185 190

Tyr Glu Asp Lys Phe Arg Asp Thr Glu Gly Leu Ile Gln Glu Ile Asn 195 200 205

Asp Leu Arg Leu Lys Val Ser Glu Met Asp Ser Glu Arg Leu Gln Tyr 210 225 220

Glu Lys Lys Leu Lys Ser Thr Lys Asp Glu Leu Ala Ser Leu Lys Glu 225 230 240

Gln Leu Glu Glu Lys Glu Ser Glu Val Lys Arg Leu Gln Glu Lys Leu 245 250 255

Val Cys Lys Met Lys Gly Glu Gly Val Glu Ile Val Asp Arg Asp Glu 260 265 270

Lys Lys Ala Val Glu Ser Leu Met Ala Ala Asn Glu Glu Lys Asp Arg 290 . 295 300

Lys Ile Glu Asp Leu Arg Gln Cys Leu Asn Arg Tyr Lys Lys Met Gln 305 310 315 320

Asp Thr Val Val Leu Ala Gln Gly Lys Lys Gly Lys Asp Gly Glu Tyr 325 330 335

Glu Glu Leu Asn Ser Ser Ser Ile Ser Ser Leu Leu Asp Ala Gln 340 345 350

Gly Phe Ser Asp Leu Glu Lys Ser Pro Ser Pro Thr Pro Val Met Gly 355 360 .365

Ser Pro Ser Cys Asp Pro Phe Asn Thr Ser Val Pro Glu Glu Phe His 370 380

Thr Thr Ile Leu Gln Val Ser Ile Pro Ser Leu Leu Pro Ala Thr Val 385 390 395 400

Ser Met Glu Thr Ser Glu Lys Ser Lys Leu Thr Pro Lys Pro Glu Thr 405 410 415

Ser Phe Glu Glu Asn Asp Gly Asn Ile Ile Leu Gly Ala Thr Val Asp 420 425 430 Thr Gln Leu Arg Asp Lys Leu Leu Thr Ser Ser Leu Gln Lys Ser Ser 435  $\phantom{\bigg|}440\phantom{\bigg|}$ Ser Leu Gly Asn Leu Lys Lys Glu Thr Ser Asp Gly Glu Lys Glu Thr 450 460Ile Gln Lys Thr Ser Glu Asp Arg Ala Pro Ala Glu Ser Arg Pro Phe 465 470 475 480 Gly Thr Leu Pro Pro Arg Pro Pro Gly Gln Asp Thr Ser Met Asp Asp 495 495Asn Pro Phe Gly Thr Arg Lys Val Arg Ser Ser Phe Gly Arg Gly Phe 500 505 510Phe Lys Ile Lys Ser Asn Lys Arg Thr Ala Ser Ala Pro Asn Leu Asp 515 525Arg Lys Arg Ser Ala Ser Ala Pro Thr Leu Ala Glu Thr Glu Lys Glu 530 540 Thr Ala Ala His Leu Asp Leu Ala Gly Ala Ser Ser Arg Pro Lys Asp 545 550 560 Ser Gln Arg Asn Ser Pro Phe Gln Ile Pro Pro Pro Ser Pro Asp Ser 565 570 575Lys Lys Lys Ser Arg Gly Ile Met Lys Leu Phe Gly Lys Leu Arg Arg 580 585 590Ser Gln Ser Thr Thr Phe Asn Pro Asp Asp Met Ser Glu Pro Glu Phe 595 600 605 Lys Arg Gly Gly Thr Arg Ala Thr Ala Gly Pro Arg Leu Gly Trp Ser 610 620 Arg Asp Leu Gly Gln Ser Asn Ser Asp Leu Asp Met Pro Phe Ala Lys 625 630 635 640 Trp Thr Lys Glu Gln Val Cys Asn Trp Leu Met Glu Gln Gly Leu Gly 645 650 655Ser Tyr Leu Asn Ser Gly Lys His Trp Ile Ala Ser Gly Gln Thr Leu 660 665 670Leu Gln Ala Ser Gln Gln Asp Leu Glu Lys Glu Leu Gly Ile Lys His 675 680 685 Ser Leu His Arg Lys Lys Leu Gln Leu Ala Leu Gln Ala Leu Gly Ser 690 700Glu Glu Glu Thr Asn His Gly Lys Leu Asp Phe Asn Trp Val Thr Arg 705 710 715 720 Trp Leu Asp Asp Ile Gly Leu Pro Gln Tyr Lys Thr Gln Phe Asp Glu
725 730 735

Gly Arg Val Asp Gly Arg Met Leu His Tyr Met Thr Val Asp Asp Leu 740 745 750

Leu Ser Leu Lys Val Val Ser Val Leu His His Leu Ser Ile Lys Arg 755 760 765

Ala Ile Gln Val Leu Arg Ile Asn Asn Phe Glu Pro Asn Cys Leu Arg 770 780

Arg Arg Pro Ser Asp Glu Asn Thr Ile Ala Pro Ser Glu Val Gln Lys 785 790 795 800

Trp Thr Asn His Arg Val Met Glu Trp Leu Arg Ser Val Asp Leu Ala 805 610 815

Glu Tyr Ala Pro Asn Leu Arg Gly Ser Gly Val His Gly Gly Leu Met 820 825 830

Val Leu Glu Pro Arg Phe Asn  $\dot{\text{Val}}$  Glu Thr Met Ala Gln Leu Leu Asn 835 840 845

Ile Pro Pro Asn Lys Thr Leu Leu Arg Arg His Leu Ala Thr His Phe 850 855 860

Asn Leu Leu Ile Gly Ala Glu Ala Gln His Gln Lys Arg Asp Ala Met 865 870 875 880

Glu Leu Pro Asp Tyr Val Leu Leu Thr Ala Thr Ala Lys Val Lys Pro 885 890 895

Lys Lys Leu Ala Phe Ser Asn Phe Gly Asn Leu Arg Lys Lys Gln  $900 \hspace{1.5cm} 905 \hspace{1.5cm} 910$ 

Glu Asp Gly Glu Glu Tyr Val Cys Pro Met Glu Leu Gly Gln Ala Ser 915 920 925

Gly Ser Ala Ser Lys Lys Gly Phe Lys Pro Gly Leu Asp Met Arg Leu 930 940

Tyr Glu Glu Asp Asp Leu Asp Arg Leu Glu Glu Met Glu Asp Ser Glu 945 950 950 960

Gly Thr Val Arg Gln Ile Gly Ala Phe Ser Glu Gly Ile Asn Asn Leu 965 970 975

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Ser Pro Ser Ala Ser Ile Thr Asp Glu Asp Ser Asn Val 995 1000 1005

<210> 112

<211> 2871 <212> PRT

<213> Homo sapiens

<400> 112

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Met Ile Arg Ala Glu Ser Gly Pro Asp Leu Arg Tyr Glu Val Thr Ser 20 25 30

Gly Gly Gly Thr Ser Arg Met Tyr Tyr Ser Arg Arg Gly Val Ile  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Thr Asp Gln Asn Ser Asp Gly Tyr Cys Gln Thr Gly Thr Met Ser Arg 50 60

His Gln Asn Gln Asn Thr Ile Gln Glu Leu Leu Gln Asn Cys Ser Asp 65 70 75 80

Cys Leu Met Arg Ala Glu Leu Ile Val Gln Pro Glu Leu Lys Tyr Gly 85 90 95

Asp Gly Ile Gln Leu Thr Arg Ser Arg Glu Leu Asp Glu Cys Phe Ala 100 105 110

Gln Ala Asn Asp Gln Met Glu Ile Leu Asp Ser Leu Ile Arg Glu Met 115 120 125

Arg Gln Met Gly Gln Pro Cys Asp Ala Tyr Gln Lys Arg Leu Leu Gln 130 135 140

Leu Gln Glu Gln Met Arg Ala Leu Tyr Lys Ala Ile Ser Val Pro Arg 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}160\phantom{\bigg|}$ 

Val Arg Arg Ala Ser Ser Lys Gly Gly Gly Gly Tyr Thr Cys Gln Ser 165 170 175

Gly Ser Gly Trp Asp Glu Phe Thr Lys His Val Thr Ser Glu Cys Leu 180  $$185\$ 

Gly Trp Met Arg Gln Gln Arg Ala Glu Met Asp Met Val Ala Trp Gly 195 200 205

Val Asp Leu Ala Ser Val Glu Gln His Ile Asn Ser His Arg Gly Ile 210 215 220

His Asn Ser Ile Gly Asp Tyr Arg Trp Gln Leu Asp Lys Ile Lys Ala 225 230 240

Asp Leu Arg Glu Lys Ser Ala Ile Tyr Gln Leu Glu Glu Glu Tyr Glu 245  $\phantom{\bigg|}250\phantom{\bigg|}250\phantom{\bigg|}$ 

Asn Leu Leu Lys Ala Ser Phe Glu Arg Met Asp His Leu Arg Gln Leu 260 265 270

Gln Asn Ile Ile Gln Ala Thr Ser Arg Glu Ile Met Trp Ile Asn Asp 275 280 285

Cys Glu Glu Glu Glu Leu Leu Tyr Asp Trp Ser Asp Lys Asn Thr Asn 290 295 300

Ile Ala Gln Lys Gln Glu Ala Phe Ser Ile Arg Met Ser Gln Leu Glu 305 310 315 320

Val Lys Glu Lys Glu Leu Asn Lys Leu Lys Gln Glu Ser Asp Gln Leu 325 330 335

Val Leu Asn Gln His Pro Ala Ser Asp Lys Ile Glu Ala Tyr Met Asp 340 345 350Thr Leu Gln Thr Gln Trp Ser Trp Ile Leu Gln Ile Thr Lys Cys Ile 355 360 365 Asp Val His Leu Lys Glu Asn Ala Ala Tyr Phe Gln Phe Phe Glu Glu 370 375 380 Ala Gln Ser Thr Glu Ala Tyr Leu Lys Gly Leu Gln Asp Ser Ile Arg 385 390 395 400 Lys Lys Tyr Pro Cys Asp Lys Asn Met Pro Leu Gln His Leu Leu Glu 405 410 415Gln Ile Lys Glu Leu Glu Lys Glu Arg Glu Lys Ile Leu Glu Tyr Lys 420 425 430Arg Gln Val Gln Asn Leu Val Asn Lys Ser Lys Lys Ile Val Gln Leu 435 440 445 Lys Pro Arg Asn Pro Asp Tyr Arg Ser Asn Lys Pro Ile Ile Leu Arg 450 455 460 Ala Leu Cys Asp Tyr Lys Gln Asp Gln Lys Ile Val His Lys Gly Asp 465 470 475 480 Glu Cys Ile Leu Lys Asp Asn Asn Glu Arg Ser Lys Trp Tyr Val Thr 485 490 495 Gly Pro Gly Gly Val Asp Met Leu Val Pro Ser Val Gly Leu Ile Ile 500 505 510 Pro Pro Pro Asn Pro Leu Ala Val Asp Leu Ser Cys Lys Ile Glu Gln 515 520 525Tyr Tyr Glu Ala Ile Leu Ala Leu Trp Asn Gln Leu Tyr Ile Asn Met 530 535 540Lys Ser Leu Val Ser Trp His Tyr Cys Met Ile Asp Ile Glu Lys Ile 545  $\phantom{\bigg|}550\phantom{\bigg|}550\phantom{\bigg|}555\phantom{\bigg|}560\phantom{\bigg|}$ Arg Ala Met Thr Ile Ala Lys Leu Lys Thr Met Arg Gln Glu Asp Tyr 565 570 575Met Lys Thr Ile Ala Asp Leu Glu Leu His Tyr Gln Glu Phe Ile Arg 580 585 590Asn Ser Gln Gly Ser Glu Met Phe Gly Asp Asp Asp Lys Arg Lys Ile 595 600 605Gln Ser Gln Phe Thr Asp Ala Gln Lys His Tyr Gln Thr Leu Val Ile  $610 \hspace{1.5cm} 615 \hspace{1.5cm} 620$ Gln Leu Pro Gly Tyr Pro Gln His Gln Thr Val Thr Thr Thr Glu Ile 625 630 635 640Thr His His Gly Thr Cys Gln Asp Val Asn His Asn Lys Val Ile Glu

Page 145

645 650 655

Thr Asn Arg Glu Asn Asp Lys Gln Glu Thr Trp Met Leu Met Glu Leu 660 665 670 Gln Lys Ile Arg Arg Gln Ile Glu His Cys Glu Gly Arg Met Thr Leu 675 680 685 Lys Asn Leu Pro Leu Ala Asp Gln Gly Ser Ser His His Ile Thr Val Lys Ile Asn Glu Leu Lys Ser Val Gln Asn Asp Ser Gln Ala Ile Ala 705 710 715 720 Glu Val Leu Asn Gln Leu Lys Asp Met Leu Ala Asn Phe Arg Gly Ser 725 730 735 Glu Lys Tyr Cys Tyr Leu Gln Asn Glu Val Phe Gly Leu Phe Gln Lys 740 745 750 Leu Glu Asn Ile Asn Gly Val Thr Asp Gly Tyr Leu Asn Ser Leu Cys 755 760 765Thr Val Arg Ala Leu Leu Gln Ala Ile Leu Gln Thr Glu Asp Met Leu 770 780 Lys Val Tyr Glu Ala Arg Leu Thr Glu Glu Glu Thr Val Cys Leu Asp 785 790 795 800 Leu Asp Lys Val Glu Ala Tyr Arg Cys Gly Leu Lys Lys Ile Lys Asn 805 810 815 Asp Leu Asn Leu Lys Lys Ser Leu Leu Ala Thr Met Lys Thr Glu Leu 820 825 830 Gln Lys Ala Gln Gln Ile His Ser Gln Thr Ser Gln Gln Tyr Pro Leu 835 840 845 Tyr Asp Leu Asp Leu Gly Lys Phe Gly Glu Lys Val Thr Gln Leu Thr 850 855 860 Asp Arg Trp Gln Arg Ile Asp Lys Gln Ile Asp Phe Arg Leu Trp Asp 865 870 875 880 Leu Glu Lys Gln Ile Lys Gln Leu Arg Asn Tyr Arg Asp Asn Tyr Gln 885 . 890 895 Ala Phe Cys Lys Trp Leu Tyr Asp Arg Lys Arg Arg Gln Asp Ser Leu 900 905 910 Glu Ser Met Lys Phe Gly Asp Ser Asn Thr Val Met Arg Phe Leu Asn 915 920 925 Glu Gln Lys Asn Leu His Ser Glu Ile Ser Gly Lys Arg Asp Lys Ser 930 935 940 Glu Glu Val Gln Lys Ile Ala Glu Leu Cys Ala Asn Ser Ile Lys Asp 945 950 955 960

Tyr Glu Leu Gln Leu Ala Ser Tyr Thr Ser Gly Leu Glu Thr Leu Leu 965 970 975

As nIle Pro Ile Lys Arg Thr Met Ile Gln Ser Pro Ser Gly Val Ile 980 985 990

Leu Gln Glu Ala Ala Asp Val His Ala Arg Tyr Ile Glu Leu Leu Thr 995 1000 1005

Arg Ser Gly Asp Tyr Tyr Arg Phe Leu Ser Glu Met Leu Lys Ser 1010 1015 1020

Leu Glu Asp Leu Lys Leu Lys Asn Thr Lys Ile Glu Val Leu Glu 1025  ${}^{\circ}$  1030  ${}^{\circ}$  1035  ${}^{\circ}$ 

Glu Glu Leu Arg Leu Ala Arg Asp Ala Asn Ser Glu Asn Cys Asn 1040 1045 1050

Lys Asn Lys Phe Leu Asp Gln Asn Leu Gln Lys Tyr Gln Ala Glu  $1055 \hspace{1.5cm} 1060 \hspace{1.5cm} 1065$ 

Cys Ser Gln Phe Lys Ala Lys Leu Ala Ser Leu Glu Glu Leu Lys 1070 1075 1080

Arg Gln Ala Glu Leu Asp Gly Lys Ser Ala Lys Gln Asn Leu Asp 1085 1090 1095

Leu Thr Tyr Glu Ile Glu Asp Glu Lys Arg Arg Arg Lys Ser Val 1115 1120 1125

Glu Asp Arg Phe Asp Gln Gln Lys Asn Asp Tyr Asp Gln Leu Gln 1130 1140

Lys Ala Arg Gln Cys Glu Lys Glu Asn Leu Gly Trp Gln Lys Leu 1145 1150 1155

Glu Ser Glu Lys Ala Ile Lys Glu Lys Glu Tyr Glu Ile Glu Arg 1160 1165 1170

Leu Arg Val Leu Leu Gln Glu Glu Gly Thr Arg Lys Arg Glu Tyr 1175 1180 1185

Glu Asn Glu Leu Ala Lys Val  $\mbox{Arg}$  Asn His Tyr Asn Glu Glu Met 1190 1200

Ser Asn Leu Arg Asn Lys Tyr Glu Thr Glu Ile Asn Ile Thr Lys  $1205 \hspace{1.5cm} 1210 \hspace{1.5cm} 1215$ 

Thr Thr Ile Lys Glu Ile Ser Met Gln Lys Glu Asp Asp Ser Lys 1220 1225 1230

Asn Leu Arg Asn Gln Leu Asp Arg Leu Ser Arg Glu Asn Arg Asp 1235 1240 1245

Leu Lys Asp Glu Ile Val Arg Leu Asn Asp Ser Ile Leu Gln Ala 1250 1260

Thr	Glu 1265		Arg	Arg	Arg	Ala 1270		Glu	Asn	Ala	Leu 1275	Gln	Gln	Lys
Ala	Cys 1280		Ser	Glu		Met 1285		Lys	Lys	Gln	His 1290	Leu	Glu	Ile
Glu	Leu 1295		Gln	Val		Gln 1300		Arg	Ser		Asp 1305		Ala	Arg
His	Lys 1310		Ser	Leu	Glu	Glu 1315	Ala	Ala	Lys	Thr	Ile 1320		Asp	Lys
Asn	Lys 1325	Glu	Ile	Glu	Arg	Leu 1330	Lys	Ala	Glu		Gln 1335		Glu	Ala
Lys	Arg 1340	Arg	Trp	Glu	Tyr	Glu 1345		Glu	Leu	Ser	Lys 1350	Val	Arg	Asn
Asn	Туг 1355		Glu	Glu		Ile 1360	Ser	Leu	Lys	Asn	Gln 1365		Glu	Thr
Glu	Ile 1370		Ile	Thr		Thr 1375		Ile	His		Leu 1380		Met	Gln
Lys	Glu 1385		Asp	Thr		Gly 1390		Arg	Ala	Gln	Ile 1395		Asn	Leu
Thr	Arg 1400		Asn	Arġ	Ser	Leu 1405	Ser	Glu	Glu		Lys 1410		Leu	Lys
Asn	Thr 1415		Thr	Gln	Thr	Thr 1420	Glu	Asn	Leu	Arg	Arg 1425	Val	Glu	Glu
Asp	Ile 1430	Gln	Gln	Gln		Ala 1435	Thr	Gly	Ser	Glu	Val 1440	Ser	Gln	Arg
	Gln 1445		Leu	Glu		Glu 1450		Arg	Gln		Thr 1455		Met	Arg
Thr	Glu 1460	Glu	Ser	Val	Arg	Tyr 1465	Lys	Gln	Ser	Leu	Asp 1470	Asp	Ala	Ala
Lys	Thr 1475	Ile	Gln	Asp	Lys	Asn 1480	Lys	Glu	Ile	Glu	Arg 1485	Leu	Lys	Gln
Leu	Ile 1490	Asp	Lys	Glu	Thr	Asn 1495	Asp	Arg	Lys	Cys	Leu 1500	Glu	Asp	Glu
Asn	Ala 1505	Arg	Leu	Gln	Arg	Val 1510	Gln	Tyr	Asp	Leu	Gln 1515	Lys	Ala	Asn
Ser	Ser 1520	Ala	Thr	Glu	Thr	Ile 1525	Asn	Lys	Leu	Lys	Val 1530	Gln	Glu	Gln
Glu	Leu 1535	Thr	Arg	Leu	Arg	Ile 1540	Asp	Tyr	Glu	Arg	Val 1545	Ser	Gln	Glu
Arg	Thr 1550	Val	Lys	Asp	Gln	Asp 1555	Ile	Thr	Arg		Gln 1560 de 14			Leu

Lys Glu Leu Gln Leu Gln Lys Gln Lys Val Glu Glu Glu Leu Asn 1565 1570 1575 Arg Leu Lys Arg Thr Ala Ser Glu Asp Ser Cys Lys Arg Lys Lys 1580 1585 Leu Glu Glu Glu Leu Glu Gly Met Arg Arg Ser Leu Lys Glu Gln 1595 1600 1605 Ala Ile Lys Ile Thr Asn Leu Thr Gln Gln Leu Glu Gln Ala Ser 1610 1620Ile Val Lys Lys Arg Ser Glu Asp Asp Leu Arg Gln Gln Arg Asp 1625 1630 Val Leu Asp Gly His Leu Arg Glu Lys Gln Arg Thr Gln Glu Glu 1640 1650Leu Arg Arg Leu Ser Ser Glu Val Glu Ala Leu Arg Arg Gln Leu 1655 1660 1665 Leu Gln Glu Gln Glu Ser Val Lys Gln Ala His Leu Arg Asn Glu 1670 1675 1680 His Phe Gln Lys Ala Ile Glu Asp Lys Ser Arg Ser Leu Asn Glu 1685 1690 1695 Ser Lys Ile Glu Ile Glu Arg Leu Gln Ser Leu Thr Glu Asn Leu 1700 1705 1710 Thr Lys Glu His Leu Met Leu Glu Glu Glu Leu Arg Asn Leu Arg 1715 1720 1725 Leu Glu Tyr Asp Asp Leu Arg Arg Gly Arg Ser Glu Ala Asp Ser 1730 1735 1740 Asp Lys Asn Ala Thr Ile Leu Glu Leu Arg Ser Gln Leu Gln Ile 1745  $\phantom{\bigg|}$  1750  $\phantom{\bigg|}$  1755 Ser Asn Asn Arg Thr Leu Glu Leu Gln Gly Leu Ile Asn Asp Leu 1760 1765 1770 Gln Arg Glu Arg Glu Asn Leu Arg Gln Glu Ile Glu Lys Phe Gln 1775 1780 1785 Lys Gln Ala Leu Glu Ala Ser Asn Arg Ile Gln Glu Ser Lys Asn 1790 1795 1800 Gln Cys Thr Gln Val Val Gln Glu Arg Glu Ser Leu Leu Val Lys 1805 1810 1815 Ile Lys Val Leu Glu Gln Asp Lys Ala Arg Leu Gln Arg Leu Glu 1820 1830 Asp Glu Leu Asn Arg Ala Lys Ser Thr Leu Glu Ala Glu Thr Arg 1835 1840 1845 Val Lys Gln Arg Leu Glu Cys Glu Lys Gln Gln Ile Gln Asn Asp Page 149

1850 1855 1860

Leu Asn Gln Trp Lys Thr Gln Tyr Ser Arg Lys Glu Glu Ala Ile 1865 1870

- Arg Lys Ile Glu Ser Glu Arg Glu Lys Ser Glu Arg Glu Lys Asn 1880 1885 1890
- Ser Leu Arg Ser Glu Ile Glu Arg Leu Gln Ala Glu Ile Lys Arg 1895 1900 1905
- Ile Glu Glu Arg Cys Arg Arg Lys Leu Glu Asp Ser Thr Arg Glu 1910 1915 1920
- Thr Gln Ser Gln Leu Glu Thr Glu Arg Ser Arg Tyr Gln Arg Glu 1925 1930 1935
- Ile Asp Lys Leu Arg Gln Arg Pro Tyr Gly Ser His Arg Glu Thr 1940 \$1940\$
- Gln Thr Glu Cys Glu Trp Thr Val Asp Thr Ser Lys Leu Val Phe 1955 1960 1965
- Asp Gly Leu Arg Lys Lys Val Thr Ala Met Gln Leu Tyr Glu Cys 1970 1980
- Gln Leu Ile Asp Lys Thr Thr Leu Asp Lys Leu Leu Lys Gly Lys 1985 1990 1995
- Lys Ser Val Glu Glu Val Ala Ser Glu Ile Gln Pro Phe Leu Arg 2000 2005 2010
- Gly Ala Gly Ser Ile Ala Gly Ala Ser Ala Ser Pro Lys Glu Lys 2015 2020 2025
- Tyr Ser Leu Val Glu Ala Lys Arg Lys Lys Leu Ile Ser Pro Glu 2030 2040
- Ser Thr Val Met Leu Leu Glu Ala Gln Ala Ala Thr Gly Gly Ile 2045 2055
- Ile Asp Pro His Arg Asn Glu Lys Leu Thr Val Asp Ser Ala Ile 2060 2065
- Ala Arg Asp Leu Ile Asp Phe Asp Asp Arg Gln Gln Ile Tyr Ala 2075 2080 2085
- Ala Glu Lys Ala Ile Thr Gly Phe Asp Asp Pro Phe Ser Gly Lys 2090 2095 2100
- Thr Val Ser Val Ser Glu Ala Ile Lys Lys Asn Leu Ile Asp Arg 2105 2110 2115
- Glu Thr Gly Met Arg Leu Leu Glu Ala Gln Ile Ala Ser Gly Gly 2120 2125 2130
- Val Val Asp Pro Val Asn Ser Val Phe Leu Pro Lys Asp Val Ala 2135 2140 2145

 Leu Ala 2150
 Arg Gly Leu Ile Asp 2155
 Arg Asp Leu Tyr Arg 2160
 Ser Leu Asn 2160

 Asp Pro 2165
 Arg Asp Ser Gln Lys 2170
 Asn Phe Val Asp Pro 2175
 Val Thr Lys 2180

 Lys Lys 2180
 Val Ser Tyr Val Gln 2185
 Leu Lys Glu Arg Cys 2190
 Arg Ile Glu 2180

 Pro His 2195
 Thr Gly Leu Leu Leu Leu Leu Ser Val Gln Lys 2205
 Arg Ser Met 2205

 Ser Phe 2195
 Gln Gly Ile Arg Gln Pro Val Thr Val Thr 2205
 Glu Leu Val 2215

 Asp Ser 2210
 Gly Ile Leu Arg Pro 22215
 Ser Thr Val Asn Glu 2235
 Leu Glu Ser 2225

 Gly Gln 210
 Ile Ser Tyr Asp Glu 2245
 Val Gly Glu Arg Ile 2255
 Lys Asp Phe 2255

 Leu Gln 2240
 Ser Ser Cys Ile 2260
 Ala Gly Ile Tyr Asn 2265
 Glu Thr Thr 2265

 Lys Gln 2270
 Lys Leu Gly Ile Tyr 2275
 Glu Ala Met Lys Ile 2280
 Gly Leu Val 2290

 Arg Pro 2285
 Gly Thr Ala Leu Glu Leu Leu Glu Ala Glu Ala Gly Ile Glu Pro Val Glu 2300
 Pro Val Glu 2310

 Gly Phe 2300
 Ile Val Asp Pro Val 2305
 Ser Asn Leu Arg Leu Pro 2310
 Pro Val Glu Lys 2325

 Leu Leu Leu Ser Ala Glu Arg Ala 2335
 Val Thr Gly Tyr Asn Asp Asp Pro Glu 2340

Ile Glu Lys Gly His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala 2360 2365 2370

Thr Gly Gly Ile Ile Asp Pro Lys Glu Ser His Arg Leu Pro Val 2375  $\phantom{\bigg|}2380\phantom{\bigg|}$  2380  $\phantom{\bigg|}2385\phantom{\bigg|}$ 

Asp Ile Ala Tyr Lys Arg Gly Tyr Phe Asn Glu Glu Leu Ser Glu 2390 2395 2400

Ile Leu Ser Asp Pro Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro 2405 2415

Asn Thr Glu Glu Asn Leu Thr Tyr Leu Gln Leu Lys Glu Arg Cys 2420 2425 2430

Ile Lys Asp Glu Glu Thr Gly Leu Cys Leu Pro Leu Lys Glu 2435 2440 2445

Lys	Lys 2450		Gln	Val	Gln	Thr 2455	Ser	Gln	Lys	Asn	Thr 2460	Leu	Arg	Lys
Arg	Arg 2465	Val	Val	Ile	Val	Asp 2470	Pro	Glu	Thr	Asn	Lys 2475	Glu	Met	Ser
Val	Gln 2480	Glu	Ala	Tyr	Lys	Lys 2485	Gly	Leu	Ile	Asp	Tyr 2490	Glu	Thr	Phe
Lys	Glu 2495	Leu	Cys	Glu	Gln	Glu 2500	Cys	Glu	Trp	Glu	Glu 2505	Ile	Thr	Ile
Thr	Gly 2510	Ser	Asp	Gly	Ser	Thr 2515	Arg	Val	Val	Leu	Val 2520	Asp	Arg	Lys
Thr	Gly 2525		Gln	Tyr	Asp	Ile 2530		Asp	Ala	Ile	Asp 2535	Lys	Gly	Leu
Val	Asp 2540	Arg	Lys	Phe	Phe	Asp 2545	Gln	Tyr	Arg	Ser	Gly 2550	Ser	Leu	Ser
Leu	Thr 2555	Gln	Phe	Ala	Asp	Met 2560	Ile	Ser	Leu	Lys	Asn 2565	Gly	Val	Gly
Thr	Ser 2570		Ser	Met	Gly	Ser 2575	Gly	Val	Ser	Asp	Asp 2580	Val	Phe	Ser
Ser	Ser 2585	Arg	His	Glu	Ser	Val 2590	Ser	Lys	Ile	Ser	Thr 2595	Ile	Ser	Ser
Val	Arg 2600		Leu	Thr	Ile	Arg 2605	Ser	Ser	Ser	Phe	Ser 2610	Asp	Thr	Leu
Glu	Glu 2615		Ser	Pro	Ile	Ala 2620	Ala	Ile	Phe	Asp	Thr 2625	Glu	Asn	Leu
Glu	Lys 2630	Ile	Ser	Ile	Thr	Glu 2635	Gly	Ile	Glu	Arg	Gly 2640	Ile	Val	Asp
Ser	Ile 2645	Thr	Gly	Gln	Arg	Leu 2650	Leu	Glu	Ala	Gln	Ala 2655	Cys	Thr	Gly
Gly	Ile 2660		His	Pro	Thr	Thr 2665	Gly	Gln	Lys	Leu	Ser 2670	Leu	Gln	Asp
Ala	Val 2675	Ser	Gln	Gly	Val	Ile 2680		Gln	Asp	Met	Ala 2685	Thr	Ser	Val
Lys	Pro 2690		Gln	Гуз	Ala	Phe 2695	Ile	Gly	Phe	Glu	Gly 2700	Val	Lys	Gly
Lys	Lys 2705	Lys	Met	Ser	Ala	Ala 2710	Glu	Ala	Val	Lys	Glu 2715	Lys	Trp	Leu
Pro	Tyr 2720	Glu	Ala	Gly	Gln	Arg 2725		Leu	Glu	Phe	Gln 2730	Tyr	Leu	Thr
Gly	Gly 2735	Leu	Val	Asp	Pro	Glu 2740		His	Gly		Ile 2745 ge 15		Thr	Glu

Glu Ala Ile Arg Lys Gly Phe Ile Asp Gly Arg Ala Ala Gln Arg 2750 2755 2760

Leu Gln Asp Thr Ser Ser Tyr Ala Lys Ile Leu Thr Cys Pro Lys 2765 2770.

Val Glu Asp Ile Thr Gly Leu Arg Leu Leu Glu Ala Ala Ser Val 2795 2800 2805

Ser Ser Lys Gly Leu Pro Ser Pro Tyr Asn Met Ser Ser Ala Pro 2810 2815 2820

Gly Ser Arg Ser Gly Ser Arg Ser Gly Ser Arg Ser Gly Ser Arg 2825 2830

Ser Gly Ser Arg Ser Gly Ser Arg Arg Gly Ser Phe Asp Ala Thr 2840

Gly Asn Ser Ser Tyr Ser Tyr Ser Tyr Ser Phe Ser Ser Ser Ser 2865

Ile Gly His 2870

<210> 113

<211> 381

<212> PRT

<213> Homo sapiens

<400> 113

Met Trp Arg Leu Met Ser Arg Phe Asn Ala Phe Lys Arg Thr Asn Thr 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Val Leu Leu Glu Lys Lys Gly Cys Ala Gly Val Ile Thr Leu Asn Arg  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Pro Lys Phe Leu Asn Ala Leu Thr Leu Asn Met Ile Arg Gln Ile Tyr 50 60

Pro Gln Leu Lys Lys Trp Glu Gln Asp Pro Glu Thr Phe Val Ile Ile 65 70 75 80

Ile Lys Gly Ala Gly Gly Lys Ala Phe Cys Ala Gly Gly Asp Ile Arg 90 95

Val Ile Ser Glu Ala Glu Lys Ala Lys Gln Lys Ile Ala Pro Val Phe 100 105 110

Phe Arg Glu Glu Tyr Met Leu Asn Asn Ala Val Gly Ser Cys Gln Lys 115 120 125

Pro Tyr Val Ala Leu Ile His Gly Ile Thr Met Gly Gly Gly Val Gly 130 135 140

Leu Ser Val His Gly Gln Phe Arg Val Ala Thr Glu Lys Cys Leu Phe 145 150 155 160

Ala Met Pro Glu Thr Ala Ile Gly Leu Phe Pro Asp Val Gly Gly Gly 165 170 175

Tyr Phe Phe Ala Thr Thr Pro Arg Lys Thr Trp Leu Leu Pro Cys Ile 180  $$185\$ 

As nGly Phe Arg Leu Lys Gly Arg Asp Val Tyr Arg Ala Gly Ile Ala 195 200 205

Thr His Phe Val Asp Ser Glu Lys Leu Ala Met Leu Glu Glu Asp Leu 210 220

Leu Ala Leu Lys Ser Pro Ser Lys Glu Asn Ile Ala Ser Val Leu Glu 225 230 235 240

Asn Tyr His Thr Glu Ser Lys Ile Asp Arg Asp Lys Ser Phe Ile Leu 245 250 250

Glu Glu His Met Asp Lys Ile Asn Ser Cys Phe Ser Ala Asn Thr Val 260 265 270

Glu Glu Ile Ile Glu Asn Leu Gln Gln Asp Gly Ser Ser Phe Ala Leu 275 280 285

Glu Gln Leu Lys Val Ile Asn Lys Met Ser Pro Thr Ser Leu Lys Ile 290 295 300

Thr Leu Arg Gln Leu Met Glu Gly Ser Ser Lys Thr Leu Gln Glu Val 305 310 315 320

Leu Thr Met Glu Tyr Arg Leu Ser Gln Ala Cys Met Arg Gly His Asp 325 330 335

Phe His Glu Gly Val Arg Ala Val Leu Ile Asp Lys Asp Gln Ser Pro 340 345 350

Lys Trp Lys Pro Ala Asp Leu Lys Glu Val Thr Glu Glu Asp Leu Asn 355 360 365

Asn His Phe Lys Ser Leu Gly Ser Ser Asp Leu Lys Phe 370 380

<210> 114 <211> 1139 <212> PRT

<213> Homo sapiens

<400> 114

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Ile Ser Gly Thr Ser Thr Ser Glu Lys Pro Asn Ser Met Asp Thr Ala 20 25 30

Asn Thr Ser Pro Phe Lys Val Pro Gly Phe Phe Ser Lys Arg Leu Lys 35 40 45

Gly Ser Ile Lys Arg Thr Lys Ser Gln Ser Lys Leu Asp Arg Asn Thr 50 55 60 Ser Phe Arg Leu Pro Ser Leu Arg Ser Thr Asp Asp Arg Ser Arg Gly 65 70 75 80 Leu Pro Lys Leu Lys Glu Ser Arg Ser His Glu Ser Leu Leu Ser Pro 85 90 95 Cys Ser Thr Val Glu Cys Leu Asp Leu Gly Arg Gly Glu Pro Val Ser 100 105 110Val Lys Pro Leu His Ser Ser Ile Leu Gly Gln Asp Phe Cys Phe Glu 115 120 125Val Thr Tyr Leu Ser Gly Ser Lys Cys Phe Ser Cys Asn Ser Ala Ser 130 135 140 Glu Arg Asp Lys Trp Met Glu Asn Leu Arg Arg Thr Val Gln Pro Asn 145 150 155 160 Lys Asp Asn Cys Arg Arg Ala Glu Asn Val Leu Arg Leu Trp Ile Ile 165 170 175Glu Ala Lys Asp Leu Ala Pro Lys Lys Lys Tyr Phe Cys Glu Leu Cys 180 185 190 Leu Asp Asp Thr Leu Phe Ala Arg Thr Thr Ser Lys Thr Lys Ala Asp 195 200 205 Asn Ile Phe Trp Gly Glu His Phe Glu Phe Phe Ser Leu Pro Pro Leu 210 215 220 Lys Asp Lys Asn Asn Tyr Val Gly Leu Val Asn Ile Pro Thr Ala Ser  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255$ Val Thr Gly Arg Gln Phe Val Glu Lys Trp Tyr Pro Val Ser Thr Pro  $260 \hspace{1cm} 265 \hspace{1cm} 270 \hspace{1cm}$ Thr Pro Asn Lys Gly Lys Thr Gly Gly Pro Ser Ile Arg Ile Lys Ser 275 280 285 Arg Phe Gln Thr Ile Thr Ile Leu Pro Met Glu Gln Tyr Lys Glu Phe 290 300Ala Glu Phe Val Thr Ser Asn Tyr Thr Met Leu Cys Ser Val Leu Glu 305 310 315 320 Pro Val Ile Ser Val Arg Asn Lys Glu Glu Leu Ala Cys Ala Leu Val 325 330 335 His Ile Leu Gln Ser Thr Gly Arg Ala Lys Asp Phe Leu Thr Asp Leu 340 345 350Val Met Ser Glu Val Asp Arg Cys Gly Glu His Asp Val Leu Ile Phe Page 155

355 360 365

Arg Glu Asn Thr Ile Ala Thr Lys Ser Ile Glu Glu Tyr Leu Lys Leu  $370 \hspace{1cm} 375 \hspace{1cm} 380$ Val Gly Gln Gln Tyr Leu His Asp Ala Leu Gly Glu Phe Ile Lys Ala 385 390 395 400 Leu Tyr Glu Ser Asp Glu Asn Cys Glu Val Asp Pro Ser Lys Cys Ser 405 410 415 Ser Ser Glu Leu Ile Asp His Gln Ser Asn Leu Lys Met Cys Cys Glu 420 425 430Leu Ala Phe Cys Lys Ile Ile Asn Ser Tyr Cys Val Phe Pro Arg Glu 435 440 445 Leu Lys Glu Val Phe Ala Ser Trp Lys Gln Gln Cys Leu Asn Arg Gly 450 455 460Lys Gln Asp Ile Ser Glu Arg Leu Ile Ser Ala Ser Leu Phe Leu Arg 465 470 475 480 Phe Leu Cys Pro Ala Ile Met Ser Pro Ser Leu Phe Asn Leu Met Gln 485 490 495 Glu Tyr Pro Asp Asp Arg Thr Ser Arg Thr Leu Thr Leu Ile Ala Lys 500 505 510Val Ile Gln Asn Leu Ala Asn Phe Ala Lys Phe Gly Asn Lys Glu Glu 515 520 525Tyr Met Ala Phe Met Asn Asp Phe Leu Glu His Glu Trp Gly Gly Met 530 540 Lys Arg Phe Leu Leu Glu Ile Ser Asn Pro Asp Thr Ile Ser Asn Thr 545 550 560 Pro Gly Phe Asp Gly Tyr Ile Asp Leu Gly Arg Glu Leu Ser Val Leu 565 570 575 His Ser Leu Leu Trp Glu Val Val Ser Gln Leu Asp Lys Gly Glu Asn 580 585 590Ser Phe Leu Gln Ala Thr Val Ala Lys Leu Gly Pro Leu Pro Arg Val 595 600 605Leu Ala Asp Ile Thr Lys Ser Leu Thr Asn Pro Thr Pro Ile Gln Gln 610  $\,$  615  $\,$  620  $\,$ Gln Leu Arg Arg Phe Thr Glu His Asn Ser Ser Pro Asn Val Ser Gly 625 630 635 640 Ser Leu Ser Ser Gly Leu Gln Lys Ile Phe Glu Asp Pro Thr Asp Ser 645 650 655 Asp Leu His Lys Leu Lys Ser Pro Ser Gln Asp Asn Thr Asp Ser Tyr  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670 \hspace{1.5cm}$ 

- Phe Arg Gly Lys Thr Leu Leu Leu Val Gln Gln Ala Ser Ser Gln Ser 675 680 685
- Met Thr Tyr Ser Glu Lys Asp Glu Arg Glu Ser Ser Leu Pro Asn Gly 690 695 700
- Arg Ser Val Ser Leu Met Asp Leu Gln Asp Thr His Ala Ala Gln Val 705 710 715 720
- Glu His Ala Ser Val Met Leu Asp Val Pro Ile Arg Leu Thr Gly Ser 725 730 735
- Gin Leu Ser Ile Thr Gln Val Ala Ser Ile Lys Gln Leu Arg Glu Thr 740 745 750
- Gln Ser Thr Pro Gln Ser Ala Pro Gln Val Arg Arg Pro Leu His Pro 755 760 765
- Ala Leu Asn Gln Pro Gly Gly Leu Gln Pro Leu Ser Phe Gln Asn Pro 770 775 780
- Val Tyr His Leu Asn Asn Pro Ile Pro Ala Met Pro Lys Ala Ser Ile 785 790 795 800
- Asp Ser Ser Leu Glu Asn Leu Ser Thr Ala Ser Ser Arg Ser Gln Ser 805 810 815
- Asn Ser Glu Asp Phe Lys Leu Ser Gly Pro Ser Asn Ser Ser Met Glu 820 825 830
- Asp Phe Thr Lys Arg Ser Thr Gln Ser Glu Asp Phe Ser Arg Arg His 835  $\phantom{\bigg|}840\phantom{\bigg|}$
- Thr Val Pro Asp Arg His Ile Pro Leu Ala Leu Pro Arg Gln Asn Ser 850 855 860
- Thr Gly Gln Ala Gln Ile Arg Lys Val Asp Gln Gly Gly Leu Gly Ala 865 870 875 880
- Arg Ala Lys Ala Pro Pro Ser Leu Pro His Ser Ala Ser Leu Arg Ser 895
- Thr Gly Ser Met Ser Val Val Ser Ala Ala Leu Val Ala Glu Pro Val 900 905 910
- Gln Asn Gly Ser Arg Ser Arg Gln Gln Ser Ser Ser Ser Arg Glu Ser 915 920 925
- Pro Val Pro Lys Val Arg Ala Ile Gln Arg Gln Gln Thr Gln Gln Val 930 935 940
- Gln Ser Pro Val Asp Ser Ala Thr Met Ser Pro Val Glu Arg Thr Ala 945 950 955 960
- Ala Trp Val Leu Asn Asn Gly Gln Tyr Glu Glu Asp Val Glu Glu Thr 965 970 975
- Glu Gln Asn Leu Asp Glu Ala Lys His Ala Glu Lys Tyr Glu Glu 980 985 990

Ile Thr Lys Leu Lys Glu Arg Leu Arg Val Ser Ser Arg Arg Leu Glu 995  $\phantom{\bigg|}$  1000  $\phantom{\bigg|}$  1005

Glu Tyr Glu Arg Arg Leu Leu Val Gln Glu Gln Gln Met Gln Lys 1010 1020

Leu Leu Leu Glu Tyr Lys Ala Arg Leu Glu Asp Ser Glu Glu Arg 1025 1030 1035

Leu Arg Arg Gln Gln Glu Glu Lys Asp Ser Gln Met Lys Ser Ile 1040 1050

Ile Ser Arg Leu Met Ala Val Glu Glu Glu Leu Lys Lys Asp His 1055 1060 1065

Ala Glu Met Gln Ala Val Ile Asp Ala Lys Gln Lys Ile Ile Asp 1070 1075 1080

Ala Gln Glu Lys Arg Ile Val Ser Leu Asp Ser Ala Asn Thr Arg 1085  $\phantom{\bigg|}1090\phantom{\bigg|}$ 

Leu Met Ser Ala Leu Thr Gln Val Lys Glu Arg Tyr Ser Met Gln 1100  $$1105\$ 

Val Arg Asn Gly Ile Ser Pro Thr Asn Pro Thr Lys Leu Ser Ile 1115  $$1120\$ 

Thr Glu Asn Gly Glu Phe Lys Asn Ser Ser Cys 1130 1135

<210> 115 <211> 165

<212> PRT

<213> Homo sapiens

<400> 115

Met Thr Leu Glu Glu Phe Ser Ala Gly Glu Gln Lys Thr Glu Arg Met
1 5 10 15

Asp Lys Val Gly Asp Ala Leu Glu Glu Val Leu Ser Lys Ala Leu Ser 20 25 30

Gln Arg Thr Ile Thr Val Gly Val Tyr Glu Ala Ala Lys Leu Leu Asn  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Val Asp Pro Asp Asn Val Val Leu Cys Leu Leu Ala Ala Asp Glu Asp 50 60

Asp Asp Arg Asp Val Ala Leu Gln Ile His Phe Thr Leu Ile Gln Ala 65 70 75 80

Phe Cys Cys Glu Asn Asp Ile Asn Ile Leu Arg Val Ser Asn Pro Gly 85 90 95

Arg Leu Ala Glu Leu Leu Leu Clu Thr Asp Ala Gly Pro Ala Ala 100 105 110

Ser Glu Gly Ala Glu Gln Pro Pro Asp Leu His Cys Val Leu Val Thr 115 120 125

Asn Pro His Ser Ser Gln Trp Lys Asp Pro Ala Leu Ser Gln Leu Ile 130 135 140

Cys Phe Cys Arg Glu Ser Arg Tyr Met Asp Gln Trp Val Pro Val Ile 145 150 150 160

Asn Leu Pro Glu Arg 165

<210> 116

<211> 116

<212> PRT

<213> Homo sapiens

<400> 116

Met Thr Arg Thr Arg Ala Ala Leu Leu Leu Phe Thr Ala Leu Ala Thr 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Ser Leu Gly Phe Asn Leu Asp Thr Glu Glu Leu Thr Ala Phe Arg Val $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Asp Ser Ala Gly Phe Gly Asp Ser Val Val Gln Tyr Ala Asn Ser Trp  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Val Val Val Gly Ala Pro Gln Lys Ile Thr Ala Ala Asn Gln Thr Gly 50  $\,$  55  $\,$  60  $\,$ 

Gly Leu Tyr Gln Cys Gly Tyr Ser Thr Gly Ala Cys Glu Pro IIe Gly 65 70 70 80

Leu Gln Val Pro Pro Glu Ala Val Asn Met Ser Leu Gly Leu Ser Leu 85 90 95

His His Glu Cys Gly Arg Asn Met Tyr Leu Thr Gly Leu Cys Phe Leu 115 120 125

Leu Gly Pro Thr Gln Leu Thr Gln Arg Leu Pro Val Ser Arg Gln Glu 130 135 140

Cys Pro Arg Gln Glu Gln Asp Ile Val Phe Leu Ile Asp Gly Ser Gly 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}160\phantom{\bigg|}$ 

Ser Ile Ser Ser Arg Asn Phe Ala Thr Met Met Asn Phe Val Arg Ala 165 170 175

Val Ile Ser Gln Phe Gln Arg Pro Ser Thr Gln Phe Ser Leu Met Gln 180 185 190

Phe Ser Asn Lys Phe Gln Thr His Leu Thr Phe Glu Glu Phe Arg Arg 195 200 205

Thr Ser Asn Pro Leu Ser Leu Leu Ala Ser Val His Gln Leu Gln Gly 210 220

Phe Thr Tyr Thr Ala Thr Ala Ile Gln Asn Val Val His Arg Leu Phe 225 230 235 240

His Ala Ser Tyr Gly Ala Arg Arg Asp Ala Thr Lys Ile Leu Ile Val 245 250 255

Ile Thr Asp Gly Lys Lys Glu Gly Asp Thr Leu Asp Tyr Lys Asp Val 260 265 270

Ile Pro Met Ala Asp Ala Ala Gly Ile Ile Arg Tyr Ala Ile Gly Val  $275 \hspace{1cm} 280 \hspace{1cm} 285$ 

Gly Leu Ala Phe Gln Asn Arg Asn Ser Trp Lys Glu Leu Asn Asp Ile 290 295 300

Ala Ser Lys Pro Ser Gln Glu His Ile Phe Lys Val Glu Asp Phe Asp 305 310 315 320

Ala Leu Lys Asp Ile Gln Thr Gln Leu Arg Glu Lys Ile Phe Pro Ile 325 . 330 . 335

Glu Gly Thr Glu Thr Thr Ser Ser Ser Ser Phe Glu Leu Glu Met Ala  $340 \hspace{1.5cm} 345 \hspace{1.5cm} 350$ 

Gln Glu Gly Phe Ser Ala Val Phe Thr Pro Asp Gly Pro Val Leu Gly 355 360 365

Ala Val Gly Ser Phe Thr Trp Ser Gly Gly Ala Phe Leu Tyr Pro Pro 370 375 380

Asn Met Ser Pro Thr Phe Ile Asn Met Ser Gln Glu Asn Val Asp Met 385 390 395 400

Arg Asp Ser Tyr Leu Gly Tyr Ser Thr Glu Leu Ala Leu Trp Lys Gly 405  $\phantom{\bigg|}410\phantom{\bigg|}415\phantom{\bigg|}$ 

Val Gln Ser Leu Val Leu Gly Ala Pro Arg Tyr Gln His Thr Gly Lys 420 425 430

Ala Val Ile Phe Thr Gln Val Ser Arg Gln Trp Arg Met Lys Ala Glu 435 440 445

Val Thr Gly Thr Gln Ile Gly Ser Tyr Phe Gly Pro Ser Leu Cys Ser 450 455 460

Val Asp Val Asp Ser Asp Gly Ser Thr Asp Leu Val Leu Ile Gly Pro 465 470 475 480

Pro His Tyr Tyr Glu Gln Thr Arg Gly Ala Gln Val Ser Val Cys Pro 485 490 495

Leu Pro Arg Gly Trp Arg Arg Trp Trp Cys Asp Ala Val Leu Tyr Gly 500 505 510

Glu Gln Gly His Pro Trp Gly Arg Phe Gly Ala Ala Leu Thr Val Leu 515 520 525

Gly Asp Val Asn Gly Asp Lys Leu Thr Asp Val Val Ile Gly Ala Pro 530 535 540

Gly Glu Glu Glu Asn Arg Gly Ala Val Tyr Leu Phe His Gly Val Leu 545 550 555 560

Gly Pro Ser Ile Ser Pro Ser His Ser Gln Arg Ile Ala Gly Ser Gln 565 570 575 Leu Ser Ser Arg Leu Gln Tyr Phe Gly Gln Ala Leu Ser Gly Gln 580 585 590 Asp Leu Thr Gln Asp Gly Leu Val Asp Leu Ala Val Gly Ala Arg Gly 595 600 605Gln Val Leu Leu Leu Arg Thr Arg Pro Val Leu Trp Val Gly Val Ser 610 615 620 Met Gln Phe Ile Pro Ala Glu Ile Pro Arg Ser Ala Phe Glu Cys Arg 625 630 635 640Glu Gln Val Val Ser Glu Gln Thr Leu Val Gln Ser Asn Ile Cys Leu  $645 \hspace{1.5cm} 650 \hspace{1.5cm} 655$ Tyr Ile Asp Lys Arg Ser Lys Asn Leu Leu Gly Ser Arg Asp Leu Gln 660 665 670 Ser Ser Val Thr Leu Asp Leu Ala Leu Asp Pro Gly Arg Leu Ser Pro 675 680 685 Arg Ala Thr Phe Gln Glu Thr Lys Asn Arg Ser Leu Ser Arg Val Arg 690 695 700 Val Leu Gly Leu Lys Ala His Cys Glu Asn Phe Asn Leu Leu Leu Pro 705 710 715 720 Ser Cys Val Glu Asp Ser Val Thr Pro Ile Thr Leu Arg Leu Asn Phe 725 730 735 Thr Leu Val Gly Lys Pro Leu Leu Ala Phe Arg Asn Leu Arg Pro Met 740 745 750Leu Ala Ala Asp Ala Gln Arg Tyr Phe Thr Ala Ser Leu Pro Phe Glu  $755 \hspace{1.5cm} 760 \hspace{1.5cm} 765$ Lys Asn Cys Gly Ala Asp His Ile Cys Gln Asp Asn Leu Gly Ile Ser 770 780 Phe Ser Phe Pro Gly Leu Lys Ser Leu Leu Val Gly Ser Asn Leu Glu 785 790 795 800 Leu Asn Ala Glu Val Met Val Trp Asn Asp Gly Glu Asp Ser Tyr Gly 805 810 815 Thr Thr Ile Thr Phe Ser His Pro Ala Gly Leu Ser Tyr Arg Tyr Val 820 825 830Ala Glu Gly Gln Lys Gln Gly Gln Leu Arg Ser Leu His Leu Thr Cys 835 840 845 Asp Ser Ala Pro Val Gly Ser Gln Gly Thr Trp Ser Thr Ser Cys Arg 850 855 860Ile Asn His Leu Ile Phe Arg Gly Gly Ala Gln Ile Thr Phe Leu Ala Page 161

865 870 875 880

Thr Phe Asp Val Ser Pro Lys Ala Val Leu Gly Asp Arg Leu Leu Leu 885 890 890

Thr Ala Asn Val Ser Ser Glu Asn Asn Thr Pro Arg Thr Ser Lys Thr 900 905 910

Thr Phe Gln Leu Glu Leu Pro Val Lys Tyr Ala Val Tyr Thr Val Val 915 920 925

Ser Ser His Glu Gln Phe Thr Lys Tyr Leu Asn Phe Ser Glu Ser Glu 930 940

Glu Lys Glu Ser His Val Ala Met His Arg Tyr Gln Val Asn Asn Leu 945 950 955 960

Gly Gln Arg Asp Leu Pro Val Ser Ile Asn Phe Trp Val Pro Val Glu 965  $\mathring{\phantom{0}}$  970 975

Leu Asn Gln Glu Ala Val Trp Met Asp Val Glu Val Ser Leu Pro Gln 980 985 990

Asn Pro Ser Leu Arg Cys Ser Ser Glu Lys Ile Ala Gly Pro Ala Ser 995 1000 1005

Asp Phe Leu Ala His Ile Gln Lys Asn Pro Val Leu Asp Cys Ser 1010 1015 1020

Ile Ala Gly Cys Leu Arg Phe Arg Cys Asp Val Pro Ser Phe Ser 1025  $\phantom{\bigg|}$  1030  $\phantom{\bigg|}$  1035

Val Gln Glu Glu Leu Asp Phe Thr Leu Lys Gly Asn Leu Ser Phe 1040 1050

Gly Trp Val Arg Gln Ile Leu Gln Lys Lys Val Ser Val Val Ser 1055 1060 1065

Val Ala Glu Ile Thr Phe Asp Thr Ser Val Tyr Ser Gln Leu Pro 1070 1075 1080

Gly Gln Glu Ala Phe Met Arg Ala Gln Thr Thr Thr Val Leu Glu 1085  $\phantom{\bigg|}$  1090  $\phantom{\bigg|}$  1095

Lys Tyr Lys Val His Asn Pro Thr Pro Leu Ile Val Gly Ser Ser 1100  $$1105\$ 

Ile Gly Gly Leu Leu Leu Leu Ala Leu Île Thr Ala Val Leu Tyr 1115 1120 1125

Lys Val Gly Phe Phe Lys Arg Gln Tyr Lys Glu Met Met Glu Glu 1130 1140

Ala Asn Gly Gln Ile Ala Pro Glu Asn Gly Thr Gln Thr Pro Ser 1145 1150 1155

Pro Pro Ser Glu Lys 1160

<210> 117 <211> 335

<212> PRT

<213> Homo sapiens

<400> 117

Met Leu Gly Ile Trp Thr Leu Leu Pro Leu Val Leu Thr Ser Val Ala 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Arg Leu Ser Ser Lys Ser Val Asn Ala Gln Val Thr Asp Ile Asn Ser 20 25 30

Lys Gly Leu Glu Leu Arg Lys Thr Val Thr Thr Val Glu Thr Gln Asn  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Leu Glu Gly Leu His His Asp Gly Gln Phe Cys His Lys Pro Cys Pro 50 55 60

Pro Gly Glu Arg Lys Ala Arg Asp Cys Thr Val Asn Gly Asp Glu Pro 65 70 75 80

Asp Cys Val Pro Cys Gln Glu Gly Lys Glu Tyr Thr Asp Lys Ala His  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Phe Ser Ser Lys Cys Arg Arg Cys Arg Leu Cys Asp Glu Gly His Gly 100 105 110

Leu Glu Val Glu Ile Asn Cys Thr Arg Thr Gln Asn Thr Lys Cys Arg 115 120 125

Cys Lys Pro Asn Phe Phe Cys Asn Ser Thr Val Cys Glu His Cys Asp 130 135 140

Pro Cys Thr Lys Cys Glu His Gly Ile Ile Lys Glu Cys Thr Leu Thr 145 150 150 160

Ser Asn Thr Lys Cys Lys Glu Glu Gly Ser Arg Ser Asn Leu Gly Trp 165 170 175

Leu Cys Leu Leu Leu Leu Pro Ile Pro Leu Ile Val Trp Val Lys Arg 180 185 190

Lys Glu Val Gln Lys Thr Cys Arg Lys His Arg Lys Glu Asn Gln Gly 195 200 205

Ser His Glu Ser Pro Thr Leu Asn Pro Glu Thr Val Ala Ile Asn Leu 210 215 220

Ser Asp Val Asp Leu Ser Lys Tyr Ile Thr Thr Ile Ala Gly Val Met 225 230 235 240

Thr Leu Ser Gln Val Lys Gly Phe Val Arg Lys Asn Gly Val Asn Glu 245 250 250

Ala Lys Ile Asp Glu Ile Lys Asn Asp Asn Val Gln Asp Thr Ala Glu 260 265 270

Gln Lys Val Gln Leu Leu Arg Asn Trp His Gln Leu His Gly Lys Lys  $275 \hspace{1cm} 280 \hspace{1cm} 285$ 

Glu Ala Tyr Asp Thr Leu Ile Lys Asp Leu Lys Lys Ala Asn Leu Cys 290 295 300

Thr Leu Ala Glu Lys Ile Gln Thr Ile Ile Leu Lys Asp Ile Thr Ser 305 310 315 320

Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val 325 330 335

<210> 118

<211> 1251

<212> PRT

<213> Homo sapiens

<400> 118

Met Glu Leu Ser Asp Val Arg Cys Leu Thr Gly Ser Glu Glu Leu Tyr 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Thr Ile His Pro Thr Pro Pro Ala Gly Asp Gly Arg Ser Ala Ser Arg  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$ 

Pro Gln Arg Leu Leu Trp Gln Thr Alá Val Arg His Ile Thr Glu Gln 35 40 45

Arg Phe Ile His Gly His Arg Gly Gly Ser Gly Ser Gly Ser Gly Gly 50 55 60

Ser Gly Lys Ala Ser Asp Pro Ala Gly Gly Gly Pro Asn His His Ala 65 70 75 80

Pro Gln Leu Ser Gly Asp Ser Ala Leu Pro Leu Tyr Ser Leu Gly Pro 90 95

Gly Glu Arg Ala His Ser Thr Cys Gly Thr Lys Val Phe Pro Glu Arg  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110$ 

Ser Gly Ser Gly Ser Ala Ser Gly Ser Gly Gly Gly Gly Asp Leu Gly 115 120 125

Phe Leu His Leu Asp Cys Ala Pro Ser As<br/>n Ser Asp Phe Phe Leu As<br/>n 130 140

Gly Gly Tyr Ser Tyr Arg Gly Val Ile Phe Pro Thr Leu Arg Asn Ser 145 150 155 160

Phe Lys Ser Arg Asp Leu Glu Arg Leu Tyr Gln Arg Tyr Phe Leu Gly
165 170 175

Gln Arg Arg Lys Ser Glu Val Val Met Asn Val Leu Asp Val Leu Thr 180 185 190

Lys Leu Thr Leu Leu Val Leu His Leu Ser Leu Ala Ser Ala Pro Met 195 200 205

Asp Pro Leu Lys Gly Ile Leu Leu Gly Phe Phe Thr Gly Ile Glu Val 210 220

Val Ile Cys Ala Leu Val Val Val Arg Lys Asp Thr Thr Ser His Thr 225 230 235 240

Tyr Leu Gln Tyr Ser Gly Val Val Thr Trp Val Ala Met Thr Thr Gln 245 250 255

Ile Leu Ala Ala Gly Leu Gly Tyr Gly Leu Leu Gly Asp Gly Ile Gly 260 265 270

Tyr Val Leu Phe Thr Leu Phe Ala Thr Tyr Ser Met Leu Pro Leu Pro 275 280 285

Leu Thr Trp Ala Ile Leu Ala Gly Leu Gly Thr Ser Leu Leu Gln Val 290 295 300

Ile Leu Gln Val Val Ile Pro Arg Leu Ala Val Ile Ser Ile Asn Gln 305 310 315 320

Val Val Ala Gln Ala Val Leu Phe Met Cys Met Asn Thr Ala Gly Ile 325 330 335

Phe Ile Ser Tyr Leu Ser Asp Arg Ala Gln Arg Gln Ala Phe Leu Glu 340 345 . 350

Thr Arg Arg Cys Val Glu Ala Arg Leu Arg Leu Glu Thr Glu Asn Gln 355 360 365

Arg Gln Glu Arg Leu Val Leu Ser Val Leu Pro Arg Phe Val Val Leu 370 380

Glu Met Ilë Asn Asp Met Thr Asn Val Glu Asp Glu His Leu Gln His 385  $\phantom{\bigg|}$  390  $\phantom{\bigg|}$  395  $\phantom{\bigg|}$  400

Gln Phe His Arg Ile Tyr Ile His Arg Tyr Glu Asn Val Ser Ile Leu  $405 \hspace{1.5cm} 410 \hspace{1.5cm} 415 \hspace{1.5cm}$ 

Phe Ala Asp Val Lys Gly Phe Thr Asn Leu Ser Thr Thr Leu Ser Ala 420 425 430

Gln Glu Leu Val Arg Met Leu Asn Glu Leu Phe Ala Arg Phe Asp Arg 435  $\phantom{\bigg|}440\phantom{\bigg|}$ 

Leu Ala His Glu His His Cys Leu Arg Ile Lys Ile Leu Gly Asp Cys 450 455 460

Tyr Tyr Cys Val Ser Gly Leu Pro Glu Pro Arg Gln Asp His Ala His 465 470 475 480

Cys Cys Val Glu Met Gly Leu Ser Met IÍe Lys Thr Ile Arg Tyr Val 485 490 495

Arg Ser Arg Thr Lys His Asp Val Asp Met Arg Ile Gly Ile His Ser 500 505 510

Gly Ser Val Leu Cys Gly Val Leu Gly Leu Arg Lys Trp Gln Phe Asp 515 520 525

Val Trp Ser Trp Asp Val Asp Ile Ala Asn Lys Leu Glu Ser Gly Gly 530 540

Ile Pro Gly Arg Ile His Ile Ser Lys Ala Thr Leu Asp Cys Leu Asn 545 550 555 560

Gly Asp Tyr Asn Val Glu Glu Gly His Gly Lys Glu Arg Asn Glu Phe  $565 \hspace{1.5cm} 570 \hspace{1.5cm} 575$ 

Leu Arg Lys His Asn Ile Glu Thr Tyr Leu Ile Lys Gln Pro Glu Asp 580 585 590

Ser Leu Leu Ser Leu Pro Glu Asp Ile Val Lys Glu Ser Val Ser Ser 595 600 605

Ser Asp Arg Arg Asn Ser Gly Ala Thr Phe Thr Glu Gly Ser Trp Ser 610 615 620

Pro Glu Leu Pro Phe Asp Asn Ile Val Gly Lys Gln Asn Thr Leu Ala 625 630 635 640

Ala Leu Thr Arg Asn Ser Ile Asn Leu Leu Pro Asn His Leu Ala Gln 645 650 655

Ala Leu His Val Gln Ser Gly Pro Glu Glu Ile Asn Lys Arg Ile Glu 660 665 670

His Thr Ile Asp Leu Arg Ser Gly Asp Lys Leu Arg Arg Glu His Ile 675 680 . 685

Ser Gln Met Arg Asp Glu Val Phe Lys Ser Asn Leu Val Cys Ala Phe 705 710 715 720

Ile Val Leu Leu Phe Ile Thr Ala Ile Gln Ser Leu Leu Pro Ser Ser 725 730 735

Arg Val Met Pro Met Thr Ile Gln Phe Ser Ile Leu Ile Met Leu His 740 745 750

Ser Ala Leu Val Leu Ile Thr Thr Ala Glu Asp Tyr Lys Cys Leu Pro 755 760 765

Leu Ile Leu Arg Lys Thr Cys Cys Trp Ile Asn Glu Thr Tyr Leu Ala 770 780

Arg Asn Val Ile Ile Phe Ala Ser Ile Leu Ile Asn Phe Leu Gly Ala 785 790 795 800

Ile Leu Asn Ile Leu Trp Cys Asp Phe Asp Lys Ser Ile Pro Leu Lys 805 810 815

Asn Leu Thr Phe Asn Ser Ser Ala Val Phe Thr Asp Ile Cys Ser Tyr 820 825 830

Pro Glu Tyr Phe Val Phe Thr Gly Val Leu Ala Met Val Thr Cys Ala 835 840 845

Val Phe Leu Arg Leu Asn Ser Val Leu Lys Leu Ala Val Leu Leu Ile 850 860

Met Ile Ala Ile Tyr Ala Leu Leu Thr Glu Thr Val Tyr Ala Gly Leu 865 870 875 880

Phe Leu Arg Tyr Asp Asn Leu Asn His Ser Gly Glu Asp Phe Leu Gly 885 890 890 895

Thr Lys Glu Val Ser Leu Leu Leu Met Ala Met Phe Leu Leu Ala Val 900 905 910

Phe Tyr His Gly Gln Gln Leu Glu Tyr Thr Ala Arg Leu Asp Phe Leu 915 920 925

Trp Arg Val Gln Ala Lys Glu Glu Ile Asn Glu Met Lys Glu Leu Arg 930 935 940

Glu His Asn Glu Asn Met Leu Arg Asn Ile Leu Pro Ser His Val Ala 945 950 955 960

Arg His Phe Leu Glu Lys Asp Arg Asp Asn Glu Glu Leu Tyr Ser Gln 965 970 975

Ser Tyr Asp Ala Val Gly Val Met Phe Ala Ser Ile Pro Gly Phe Ala 980 985 990

Asp Phe Tyr Ser Gln Thr Glu Met Asn Asn Gln Gly Val Glu Cys Leu 995 1000 1005

Arg Leu Leu Asn Glu Ile Ile Ala Asp Phe Asp Glu Leu Leu Gly 1010 1020

Glu Asp Arg Phe Gln Asp Ile Glu Lys Ile Lys Thr  $\cdot$  Ile Gly Ser 1025  $\phantom{-}$  1035

Thr Tyr Met Ala Val Ser Gly Leu Ser Pro Glu Lys Gln Gln Cys 1040 1055 1050

Glu Asp Lys Trp Gly His Leu Cys Ala Leu Ala Asp Phe Ser Leu 1055 1060 1065

Ala Leu Thr Glu Ser Ile Gln Glu Ile Asn Lys His Ser Phe Asn 1070 1075 1080

Asn Phe Glu Leu Arg Ile Gly Ile Ser His Gly Ser Val Val Ala 1085 1090 1095

Gly Val Ile Gly Ala Lys Lys Pro Gln Tyr Asp Ile Trp Gly Lys 1100 1105 1110

Thr Val Asn Leu Ala Ser Arg Met Asp Ser Thr Gly Val Ser Gly 1115 1120 1125

Arg Ile Gln Val Pro Glu Glu Thr Tyr Leu Ile Leu Lys Asp Gln 1130 1140

Gly Phe Ala Phe Asp Tyr Arg Gly Glu Ile Tyr Val Lys Gly Ile 1145 1150 1155

Ser Glu Gln Glu Gly Lys Ile Lys Thr Tyr Phe Leu Leu Gly Arg 1160 1165 1170

Val Gln Pro Asn Pro Phe Ile Leu Pro Pro Arg Arg Leu Pro Gly Page 167

1175 1185 1180

Gln Tyr Ser Leu Ala Ala Val Val Leu Gly Leu Val Gln Ser Leu 1190 1195 1200

Asn Arg Gln Arg Gln Lys Gln Leu Leu Asn Glu Asn Asn Asn Thr 1205 1210 1215

Gly Ile Ile Lys Gly His Tyr Asn Arg Arg Thr Leu Leu Ser Pro 1220 1225 1230

Ser Gly Thr Glu Pro Gly Ala Gln Ala Glu Gly Thr Asp Lys Ser 1235 1240 1245

Asp Leu Pro 1250

<210> 119 <211> 143

<212> PRT

<213> Homo sapiens

<400> 119

Met Gly Lys Cys Arg Gly Leu Arg Thr Ala Arg Lys Leu Arg Ser His 1 10 15

Arg Arg Asp Gln Lys Trp His Asp Lys Gln Tyr Lys Lys Ala His Leu  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Gly Thr Ala Leu Lys Ala Asn Pro Phe Gly Gly Ala Ser His Ala Lys  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Gly Ile Val Leu Glu Lys Val Gly Val Glu Ala Lys Gln Pro Asn Ser 50 60

Ala Ile Arg Lys Cys Val Arg Val Gln Leu Ile Lys Asn Gly Lys Lys 65 70 75 80

Ile Thr Ala Phe Val Pro Asn Asp Gly Cys Leu Asn Phe Ile Glu Glu 85 90 95

Asn Asp Glu Val Leu Val Ala Gly Phe Gly Arg Lys Gly His Ala Val  $100 \,$   $105 \,$   $110 \,$ 

Gly Asp Ile Pro Gly Val Arg Phe Lys Val Val Lys Val Ala Asn Val 115 120 125

Ser Leu Leu Ala Leu Tyr Lys Gly Lys Lys Glu Arg Pro Arg Ser 130 140

<210> 120

<211> 144

<212> PRT

<213> Homo sapiens

<400> 120

Met Ala Phe Thr Phe Ala Ala Phe Cys Tyr Met Leu Ala Leu Leu Leu 1 5 10 15

Thr Ala Ala Leu Ile Phe Phe Ala Ile Trp His Ile Ile Ala Phe Asp 20 25 30

Glu Leu Lys Thr Asp Tyr Lys Asn Pro Ile Asp Gln Cys Asn Thr Leu  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Asn Pro Leu Val Leu Pro Glu Tyr Leu Ile His Ala Phe Phe Cys Val 50 60

Met Phe Leu Cys Ala Ala Glu Trp Leu Thr Leu Gly Leu Asn Met Pro 65 70 75 80

Leu Leu Ala Tyr His Ile Trp Arg Tyr Met Ser Arg Pro Val Met Ser 85 90 95

Gly Pro Gly Leu Tyr Asp Pro Thr Thr Ile Met Asn Ala Asp Ile Leu  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110$ 

Ala Tyr Cys Gl<br/>n Lys Glu Gly Trp Cys Lys Leu Ala Phe Tyr Leu Leu 115 120 125

Ala Phe Phe Tyr Tyr Leu Tyr Gly Met Ile Tyr Val Leu Val Ser Ser 130 135 140

<210> 121

211> 1516

<212> PRT

<213> Homo sapiens

<400> 121

Met Ala Pro Ala Lys Ala Thr Asn Val Val Arg Leu Leu Gly Ser 1 5 10 15

Thr Ala Leu Trp Leu Ser Gln Leu Gly Ser Gly Thr Val Ala Ala Ser 20 25 30

Lys Ser Val Thr Ala His Leu Ala Ala Lys Trp Pro Glu Thr Pro Leu  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Leu Leu Glu Ala Ser Glu Phe Met Ala Glu Glu Ser Asn Glu Lys Phe 50 60

Trp Gln Phe Leu Glu Thr Val Gln Glu Leu Ala Ile Tyr Lys Gln Thr 65 70 75 80

Glu Ser Asp Tyr Ser Tyr Tyr Asn Leu Ile Leu Lys Lys Ala Gly Gln 85 90 95

Phe Leu Asp Asn Leu His Ile Asn Leu Leu Lys Phe Ala Phe Ser Ile 100 105 110

Arg Ala Tyr Ser Pro Ala Ile Gln Met Phe Gln Gln Ile Ala Ala Asp 115 120 125

Glu Pro Pro Pro Asp Gly Cys Asn Ala Phe Val Val Ile His Lys Lys 130 135 140

His Thr Cys Lys Ile Asn Glu Ile Lys Lys Leu Leu Lys Lys Ala Ala 145 150 150 155

Ser Arg Thr Arg Pro Tyr Leu Phe Lys Gly Asp His Lys Phe Pro Thr

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Asn Lys Glu Asn Leu Pro Val Val Ile Leu Tyr Ala Glu Met Gly Thr 180 185 190 Arg Thr Phe Ser Ala Phe His Lys Val Leu Ser Glu Lys Ala Gln Asn 195 200 205 Glu Glu Ile Leu Tyr Val Leu Arg His Tyr Ile Gln Lys Pro Ser Ser 210 220Arg Lys Met Tyr Leu Ser Gly Tyr Gly Val Glu Leu Ala Ile Lys Ser 225  $\phantom{\bigg|}230\phantom{\bigg|}230\phantom{\bigg|}235\phantom{\bigg|}$ Thr Thr Val Glu Asp Glu Thr Glu Thr Asn Glu Val Gln Gly Phe Leu 260 265 270Phe Gly Lys Leu Lys Glu Ile Tyr Ser Asp Leu Arg Asp Asn Leu Thr 275 280 285 Ala Phe His Lys Tyr Leu Ile Glu Ser Asn Lys Gln Met Met Pro Leu 290 295 300 Lys Val Trp Glu Leu Gln Asp Leu Ser Phe Gln Ala Ala Ser Gln Ile 305 310 315 320 Met Ser Thr Pro Val Tyr Asp Ala Ile Lys Leu Met Lys Asp Ile Ser 325 330 335 Gln Asn Phe Pro Ile Lys Ala Arg Ser Leu Thr Arg Ile Ala Val Asn 340 345 350Gln His Met Arg Glu Glu Ile Lys Glu Asn Gln Lys Asp Leu Gln Val 355 360 365 Arg Phe Lys Ile Gln Pro Gly Asp Ala Arg Leu Phe Ile Asn Gly Leu 370 380 Arg Val Asp Met Asp Val Tyr Asp Ala Phe Ser Ile Leu Asp Met Leu 385 390 395 400 Lys Leu Glu Gly Lys Met Met Asn Gly Leu Arg Asn Leu Gly Ile Asn 415

Tyr Thr Tyr Val Leu Asp Ile Arg His Ser Ser Ile Met Trp Ile Asn 435 440 445

Gly Glu Asp Met Ser Lys Phe Leu Lys Leu Asn Ser His Ile Trp Glu 420 425 430

Asp Leu Glu Asn Asp Asp Leu Tyr Ile Thr Trp Pro Thr Ser Cys Gln 450 455 460

Lys Leu Leu Lys Pro Val Phe Pro Gly Ser Val Pro Ser Ile Arg Arg 465 470 470 480

Asn Phe His Asn Leu Val Leu Phe Ile Asp Pro Ala Gln Glu Tyr Thr Page 170

485 490 495

Leu Asp Phe Ile Lys Leu Ala Asp Val Phe Tyr Ser His Glu Val Pro 500 505 510

Leu Arg Ile Gly Phe Val Phe Ile Leu Asn Thr Asp Asp Glu Val Asp 515 520 525

Gly Ala Asn Asp Ala Gly Val Ala Leu Trp Arg Ala Phe Asn Tyr Ile 530 535 540

Ala Glu Glu Phe Asp Ile Ser Glu Ala Phe Ile Ser Ile Val His Met 545 550 555 560

Tyr Gln Lys Val Lys Lys Asp Gln Asn Ile Leu Thr Val Asp Asn Val 565 570 575

Lys Ser Val Leu Gln Asn Thr Phe Pro His Ala Asn Ile Trp Asp Ile 580 585 590

Leu Gly Ile His Ser Lys Tyr Asp Glu Glu Arg Lys Ala Gly Ala Ser 595 600 605

Phe Tyr Lys Met Thr Gly Leu Gly Pro Leu Pro Gln Ala Leu Tyr Asn 610 615 620

Gly Glu Pro Phe Lys His Glu Glu Met Asn Ile Lys Glu Leu Lys Met 625  $\,$  630  $\,$  635  $\,$  640

Ala Val Leu Gln Arg Met Met Asp Ala Ser Val Tyr Leu Gln Arg Glu 645 650 655

Val Phe Leu Gly Thr Leu Asn Asp Arg Thr Asn Ala Ile Asp Phe Leu 660 665 670

Met Asp Arg Asn Asn Val Val Pro Arg Ile Asn Thr Leu Ile Leu Arg 675 680 685

Thr Asn Gln Gln Tyr Leu Asn Leu Ile Ser Thr Ser Val Thr Ala Asp  $690 \hspace{1.5cm} 695 \hspace{1.5cm} 700$ 

Val Glu Asp Phe Ser Thr Phe Phe Phe Leu Asp Ser Gln Asp Lys Ser 705  $\phantom{\bigg|}710\phantom{\bigg|}710\phantom{\bigg|}715\phantom{\bigg|}720\phantom{\bigg|}$ 

Ala Val Ile Ala Lys Asn Met Tyr Tyr Leu Thr Gln Asp Asp Glu Ser  $725 \hspace{1cm} 730 \hspace{1cm} 735$ 

Ile Ile Ser Ala Val Thr Leu Trp Ile Ile Ala Asp Phe Asp Lys Pro 740 745 750

Ser Gly Arg Lys Leu Leu Phe Asn Ala Leu Lys His Met Lys Thr Ser 755 760 765

Val His Ser Arg Leu Gly Ile Ile Tyr Asn Pro Thr Ser Lys Ile Asn  $770 \hspace{1.5cm} 775 \hspace{1.5cm} 780$ 

Glu Glu Asn Thr Ala Ile Ser Arg Gly Ile Leu Ala Ala Phe Leu Thr 785 790 795 800

- Gln Lys Asn Met Phe Leu Arg Ser Phe Leu Gly Gln Leu Ala Lys Glu 805 810 815
- Glu Ile Ala Thr Thr Ile Tyr Ser Gly Asp Lys Ile Lys Thr Phe Leu 820 825 830
- Ile Glu Gly Met Asp Lys Asn Ala Phe Glu Lys Lys Tyr Asn Thr Val 835  $\phantom{\bigg|}$  840  $\phantom{\bigg|}$  845
- Gly Val Asn Ile Phe Arg Thr His Gln Leu Phe Cys Gln Asp Val Leu 850 855 860
- Lys Leu Arg Pro Gly Glu Met Gly Ile Val Ser Asn Gly Arg Phe Leu 865 870 880
- Gly Pro Leu Asp Glu Asp Phe Tyr Ala Glu Asp Phe Tyr Leu Leu Glu 885 890 895
- Lys Ile Thr Phe Ser Asn Leu Gly Glu Lys Ile Lys Gly Ile Val Glu 900 905 910
- Asn Met Gly Ile Asn Ala Asn Asn Met Ser Asp Phe Ile Met Lys Val 915 920 925
- Asp Ala Leu Met Ser Ser Val Pro Lys Arg Ala Ser Arg Tyr Asp Val 930 935 940
- Thr Phe Leu Arg Glu Asn His Ser Val Ile Lys Thr Asn Pro Gln Glu 945 950 950 960
- Asn Asp Met Phe Phe Asn Val Ile Ala Ile Val Asp Leu Leu Ala Arg 965 970 975
- Glu Ala Gln Lys Met Ala Gln Leu Leu Val Val Leu Gly Lys Ile Ile 980 985 990
- Asn Leu Lys Ile Lys Leu Phe Met  $\mbox{\sc Asn}$  Cys Arg Gly Arg  $\mbox{\sc Leu}$  Ser Glu  $\mbox{\sc 995}$   $\mbox{\sc 1000}$
- Ala Pro Leu Glu Ser Phe Tyr Arg Phe Val Leu Glu Pro Glu Leu 1010 1015 1020
- Met Ser Gly Ala Asn Asp Val Ser Ser Leu Gly Pro Val Ala Lys 1025 1030 1035
- Phe Leu Asp Ile Pro Glu Ser Pro Leu Leu Ile Leu Asn Met Ile 1040 1050
- Thr Pro Glu Gly Trp Leu Val Glu Thr Val His Ser Asn Cys Asp 1055 1060 1065
- Leu Asp Asn Ile His Leu Lys Asp Thr Glu Lys Thr Ala Thr Ala 1070 1075 1080
- Gly Tyr Glu Leu Glu Tyr Leu Leu Glu Glu Gln Cys Phe Asp 1085 1090 1095
- Lys Val Thr Glu Gln Pro Pro Arg Gly Leu Gln Phe Thr Leu Gly 1100 1105 1110

Thr Lys Asn Lys Pro Ala Val Val Asp Thr Ile Val Met Ala His 1115 1120 1125

- His Gly Tyr Phe Gln Leu Lys Ala Asn Pro Gly Ala Trp Ile Leu 1130 1140
- Arg Leu His Gin Gly Lys Ser Glu Asp Ile Tyr Gln Ile Val Gly 1145 1150 1155
- His Glu Gly Thr Asp Ser Gln Ala Asp Leu Glu Asp Ile Ile Val 1160 1165 1170
- Val Leu Asn Ser Phe Lys Ser Lys Ile Leu Lys Val Lys Val Lys 1175 1180 1185
- Lys Glu Thr Asp Lys Ile Lys Glu Asp Ile Leu Thr Asp Glu Asp 1190 1195 1200
- Glu Lys Thr Lys Gly Leu Trp Asp Ser Ile Lys Ser Phe Thr Val 1205 1215
- Ser Leu His Lys Glu Asn Lys Lys Glu Lys Asp Val Leu Asn Ile 1220 1230
- Phe Ser Val Ala Ser Gly His Leu Tyr Glu Arg Phe Leu Arg Ile 1235 1240 1245
- Met Met Leu Ser Val Leu Arg Asn Thr Lys Thr Pro Val Lys Phe 1250 1255 1260
- Trp Leu Leu Lys Asn Tyr Leu Ser Pro Thr Phe Lys Glu Val Ile 1265 1270 1275
- Pro His Met Ala Lys Glu Tyr Gly Phe Arg Tyr Glu Leu Val Gln 1280 1285 1290
- Tyr Arg Trp Pro Arg Trp Leu Arg Gln Gln Thr Glu Arg Gln Arg 1295 1300 1305
- Ile Ile Trp Gly Tyr Lys Ile Leu Phe Leu Asp Val Leu Phe Pro 1310 1320
- Leu Ala Val Asp Lys Ile Ile Phe Val Asp Ala Asp Gln Ile Val 1325  $\phantom{\bigg|}$  1330  $\phantom{\bigg|}$  1335
- Arg His Asp Leu Lys Glu Leu Arg Asp Phe Asp Leu Asp Gly Ala 1340 1350
- Pro Tyr Gly Tyr Thr Pro Phe Cys Asp Ser Arg Arg Glu Met Asp 1355 1360 1365
- Gly Tyr Arg Phe Trp Lys Thr Gly Tyr Trp Ala Ser His Leu Leu 1370 1375 1380
- Arg Arg Lys Tyr His Ile Ser Ala Leu Tyr Val Val Asp Leu Lys 1385 1390 1395
- Lys Phe Arg Arg Ile Gly Ala Gly Asp Arg Leu Arg Ser Gln Tyr

Gln Ala Leu Ser Gln Asp Pro Asn Ser Leu Ser Asn Leu Asp Gln 1415 1420 1425

Asp Leu Pro Asn Asn Met Ile Tyr Gln Val Ala Ile Lys Ser Leu 1430 1440

Pro Gln Asp Trp Leu Trp Cys Glu Thr Trp Cys Asp Asp Glu Ser 1445 1450 1455

Lys Gln Arg Ala Lys Thr Ile Asp Leu Cys Asn Asn Pro Lys Thr 1460 1465 1470

Lys Glu Ser Lys Leu Lys Ala Ala Ala Arg Ile Val Pro Glu Trp 1475  $\phantom{0}$  1485

Val Glu Tyr Asp Ala Glu Ile Arg Gln Leu Leu Asp His Leu Glu 1490 1495 1500

Asn Lys Lys Gln Asp Thr Ile Leu Thr His Asp Glu Leu 1505 1510 1515

<210> 122

<211> 798

<212> PRT

<213> Homo sapiens

<400> 122

Met Asn Leu Gln Pro Ile Phe Trp Ile Gly Leu Ile Ser Ser Val Cys 1  $\phantom{\Big|}$  5  $\phantom{\Big|}$  10  $\phantom{\Big|}$  15

Cys Val Phe Ala Gln Thr Asp Glu Asn Arg Cys Leu Lys Ala Asn Ala  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Lys Ser Cys Gly Glu Cys Ile Gln Ala Gly Pro Asn Cys Gly Trp Cys 35 40 45

Thr Asn Ser Thr Phe Leu Gln Glu Gly Met Pro Thr Ser Ala Arg Cys 50 60

Asp Asp Leu Glu Ala Leu Lys Lys Gly Cys Pro Pro Asp Asp Ile 65 70 75 80

Asn Arg Ser Lys Gly Thr Ala Glu Lys Leu Lys Pro Glu Asp Ile His 100 105 110

Gln Ile Gln Pro Gln Gln Leu Val Leu Arg Leu Arg Ser Gly Glu Pro 115 120 125

Gln Thr Phe Thr Leu Lys Phe Lys Arg Ala Glu Asp Tyr Pro Ile Asp 130 135 140

Leu Tyr Tyr Leu Met Asp Leu Ser Tyr Ser Met Lys Asp Asp Leu Glu 145 150 155 160

Asn Val Lys Ser Leu Gly Thr Asp Leu Met Asn Glu Met Arg Arg Ile 165 170 175

Met Pro Tyr Ile Ser Thr Thr Pro Ala Lys Leu Arg Asn Pro Cys Thr 195 200 205Ser Glu Gln Asn Cys Thr Thr Pro Phe Ser Tyr Lys Asn Val Leu Ser 210 215 220 Leu Thr Asn Lys Gly Glu Val Phe Asn Glu Leu Val Gly Lys Gln Arg 225 230 235 240 Ile Ser Gly Asn Leu Asp Ser Pro Glu Gly Gly Phe Asp Ala Ile Met 245 250 255Gln Val Ala Val Cys Gly Ser Leu Ile Gly Trp Arg Asn Val Thr Arg  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$ Leu Leu Val Phe Ser Thr Asp Ala Gly Phe His Phe Ala Gly Asp Gly 275 280 285Lys Leu Gly Gly Ile Val Leu Pro Asn Asp Gly Gln Cys His Leu Glu 290 295 300 Asn Asn Met Tyr Thr Met Ser His Tyr Tyr Asp Tyr Pro Ser Ile Ala 305 310 315 320His Leu Val Gln Lys Leu Ser Glu Asn Asn Ile Gln Thr Ile Phe Ala 325 330 335 Val Thr Glu Glu Phe Gln Pro Val Tyr Lys Glu Leu Lys Asn Leu Ile 340 345 350 Pro Lys Ser Ala Val Gly Thr Leu Ser Ala Asn Ser Ser Asn Val Ile 355 360 365 Gln Leu Ile Ile Asp Ala Tyr Asn Ser Leu Ser Ser Glu Val Ile Leu 370 375 380 Glu Asn Gly Lys Leu Ser Glu Gly Val Thr Ile Ser Tyr Lys Ser Tyr 385 390 395 400Cys Lys Asn Gly Val Asn Gly Thr Gly Glu Asn Gly Arg Lys Cys Ser  $405 \ \ 410 \ \ \ 415$ Asn Ile Ser Ile Gly Asp Glu Val Gln Phe Glu Ile Ser Ile Thr Ser 420 425 430 Asn Lys Cys Pro Lys Lys Asp Ser Asp Ser Phe Lys Ile Arg Pro Leu 435 440 445 Gly Phe Thr Glu Glu Val Glu Val Ile Leu Gln Tyr Ile Cys Glu Cys 450 455 460Glu Cys Gln Ser Glu Gly Ile Pro Glu Ser Pro Lys Cys His Glu Gly 465 470 475 480 Asn Gly Thr Phe Glu Cys Gly Ala Cys Arg Cys Asn Glu Gly Arg Val

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485 490 495

Gly Arg His Cys Glu Cys Ser Thr Asp Glu Val Asn Ser Glu Asp Met 500 505 510

Asp Ala Tyr Cys Arg Lys Glu Asn Ser Ser Glu Ile Cys Ser Asn Asn 515 520 525

Gly Glu Cys Val Cys Gly Gln Cys Val Cys Arg Lys Arg Asp Asn Thr 530 535 540

As n Glu Ile Tyr Ser Gly Lys Phe Cys Glu Cys As p As n Phe As n Cys 545 550 555 560

Asp Arg Ser Asn Gly Leu Ile Cys Gly Gly Asn Gly Val Cys Lys Cys 565 570 575

Arg Val Cys Glu Cys Asn Pro Asn Tyr Thr Gly Ser Ala Cys Asp Cys 580 585 590

Ser Leu Asp Thr Ser Thr Cys Glu Ala Ser Asn Gly Gln Ile Cys Asn 595 600 605

Gly Arg Gly Ile Cys Glu Cys Gly Val Cys Lys Cys Thr Asp Pro Lys  $610 \hspace{1.5cm} 620$ 

Phe Gln Gly Gln Thr Cys Glu Met Cys Gln Thr Cys Leu Gly Val Cys 625 630 635 640

Ala Glu His Lys Glu Cys Val Gln Cys Arg Ala Phe Asn Lys Gly Glu 645  $\,$  650  $\,$  655

Lys Lys Asp Thr Cys Thr Gln Glu Cys Ser Tyr Phe Asn Ile Thr Lys 660 665 670

Val Glu Ser Arg Asp Lys Leu Pro Gln Pro Val Gln Pro Asp Pro Val 675 680 685

Tyr Ser Val Asn Gly Asn Asn Glu Val Met Val His Val Val Glu Asn 705 710 715 720

Pro Glu Cys Pro Thr Gly Pro Asp Ile Ile Pro Ile Val Ala Gly Val 725 730 735

Val Ala Gly Ile Val Leu Ile Gly Leu Ala Leu Leu Leu Ile Trp Lys 740 745 750

Leu Leu Met Ile Ile His Asp Arg Arg Glu Phe Ala Lys Phe Glu Lys 765 760 765

Glu Lys Met Asn Ala Lys Trp Asp Thr Gly Glu Asn Pro Ile Tyr Lys 770 775 780

Ser Ala Val Thr Thr Val Val Asn Pro Lys Tyr Glu Gly Lys 785 790 795

<210> 123

<212> PRT

<213> Homo sapiens

<400> 123

Met Thr Glu Gln Met Thr Leu Arg Gly Thr Leu Lys Gly His Asn Gly 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Trp Val Thr Gln Ile Ala Thr Thr Pro Gln Phe Pro Asp Met Ile Leu 20 25 30

Ser Ala Ser Arg Asp Lys Thr Ile Ile Met Trp Lys Leu Thr Arg Asp  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Glu Thr Asn Tyr Gly Ile Pro Gln Arg Ala Leu Arg Gly His Ser His 50 55 60

Phe Val Ser Asp Val Val Ile Ser Ser Asp Gly Gln Phe Ala Leu Ser 65 70 75 80

Gly Ser Trp Asp Gly Thr Leu Arg Leu Trp Asp Leu Thr Thr Gly Thr 85 90 95

Thr Thr Arg Arg Phe Val Gly His Thr Lys Asp Val Leu Ser Val Ala  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105$ 

Phe Ser Ser Asp Asn Arg Gln Ile Val Ser Gly Ser Arg Asp Lys Thr  $115 \ 120 \ 125$ 

Ile Lys Leu Trp Asn Thr Leu Gly Val Cys Lys Tyr Thr Val Gln Asp 130  $$135\$ 

Glu Ser His Ser Glu Trp Val Ser Cys Val Arg Phe Ser Pro Asn Ser 145 150 150 155 160

Ser Asn Pro Ile Ile Val Ser Cys Gly Trp Asp Lys Leu Val Lys Val 165 170 175

Trp Asn Leu Ala Asn Cys Lys Leu Lys Thr Asn His Ile Gly His Thr 180 185 190

Gly Tyr Leu Asn Thr Val Thr Val Ser Pro Asp Gly Ser Leu Cys Ala 195  $\phantom{\bigg|}200\phantom{\bigg|}205\phantom{\bigg|}$ 

Ser Gly Gly Lys Asp Gly Gln Ala Met Leu Trp Asp Leu Asn Glu Gly 210 215 220

Lys His Leu Tyr Thr Leu Asp Gly Gly Asp Ile Ile Asn Ala Leu Cys 225 230 235 240

Phe Ser Pro Asn Arg Tyr Trp Leu Cys Ala Ala Thr Gly Pro Ser Ile 245 250 255

Lys Ile Trp Asp Leu Glu Gly Lys Ile Ile Val Asp Glu Leu Lys Gln 260 265 . 270

Glu Val Ile Ser Thr Ser Ser Lys Ala Glu Pro Pro Gln Cys Thr Ser  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285$ 

Leu Ala Trp Ser Ala Asp Gly Gln Thr Leu Phe Ala Gly Tyr Thr Asp 290 295 300

Asn Leu Val Arg Val Trp Gln Val Thr Ile Gly Thr Arg 305 310 315

<210> 124 <211> 351

<212> PRT

<213> Homo sapiens

<400> 124

Met Gln Arg Ala Leu Pro Gly Ala Arg Gln His Leu Gly Ala Ile Leu 1 10 15

Ala Ser Ala Ser Val Val Val Lys Ala Leu Cys Ala Ala Val Leu Phe 20 25 30

Leu Tyr Leu Leu Ser Phe Ala Val Asp Thr Gly Cys Leu Ala Val Thr 35 40 45

Pro Gly Tyr Leu Phe Pro Pro Asn Phe Trp Ile Trp Thr Leu Ala Thr 50 60

His Gly Leu Met Glu Gln His Val Trp Asp Val Ala Ile Ser Leu Thr 65 70 75 80

Thr Val Val Val Ala Gly Arg Leu Leu Glu Pro Leu Trp Gly Ala Leu 95 90 95

Glu Leu Leu Ile Phe Phe Ser Val Val As<br/>n Val Ser Val Gly Leu Leu 100 105 110

Gly Ala Phe Ala Tyr Leu Leu Thr Tyr Met Ala Ser Phe Asn Leu Val 115 120 125

Tyr Leu Phe Thr Val Arg Ile His Gly Ala Leu Gly Phe Leu Gly Gly 130 135 140

Val Leu Val Ala Leu Lys Gln Thr Met Gly Asp Cys Val Val Leu Arg 145 150 155 160

Val Pro Gln Val Arg Val Ser Val Met Pro Met Leu Leu Leu Ala Leu 165 170 175

Leu Leu Leu Arg Leu Ala Thr Leu Leu Gln Ser Pro Ala Leu Ala 180 185 190

Ser Tyr Gly Phe Gly Leu Leu Ser Ser Trp Val Tyr Leu Arg Phe Tyr 195 200 205

Gln Arg His Ser Arg Gly Arg Gly Asp Met Ala Asp His Phe Ala Phe 210 215 220

Ala Thr Phe Phe Pro Glu Ile Leu Gln Pro Val Val Gly Leu Leu Ala 225 230 235 240

Asn Leu Val His Ser Leu Leu Val Lys Val Lys Ile Cys Gln Lys Thr 245 250 255

Val Lys Arg Tyr Asp Val Gly Ala Pro Ser Ser Ile Thr Ile Ser Leu 260 265 270

Pro Gly Thr Asp Pro Gln Asp Ala Glu Arg Arg Arg Gln Leu Ala Leu 275 280 285

Lys Ala Leu Asn Glu Arg Leu Lys Arg Val Glu Asp Gln Ser Ile Trp 290 295 300

Pro Ser Met Asp Asp Asp Glu Glu Glu Ser Gly Ala Lys Val Asp Ser 305 310 315 320

Pro Leu Pro Ser Asp Lys Ala Pro Thr Pro Pro Gly Lys Gly Ala Ala 325 330 335

Pro Glu Ser Ser Leu Ile Thr Phe Glu Ala Ala Pro Pro Thr Leu 340  $\phantom{\bigg|}345\phantom{\bigg|}345\phantom{\bigg|}$  350

<210> 125

<211> 310

<212> PRT

<213> Homo sapiens

<400> 125

Met Arg Arg Ala Ala Leu Trp Leu Trp Leu Cys Ala Leu Ala Leu Ser 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Leu Gln Leu Ala Leu Pro Gln Ile Val Ala Thr Asn Leu Pro Pro Glu 20 25 30

Asp Gln Asp Gly Ser Gly Asp Asp Ser Asp Asn Phe Ser Gly Ser Gly 35 40 45

Ala Gly Ala Leu Gln Asp Ile Thr Leu Ser Gln Gln Thr Pro Ser Thr 50 60

Trp Lys Asp Thr Gln Leu Leu Thr Ala Ile Pro Thr Ser Pro Glu Pro 65 70 75 80

Thr Gly Leu Glu Ala Thr Ala Ala Ser Thr Ser Thr Leu Pro Ala Gly  $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Glu Gly Pro Lys Glu Gly Glu Ala Val Val Leu Pro Glu Val Glu Pro 100 105 110

Gly Leu Thr Ala Arg Glu Gln Glu Ala Thr Pro Arg Pro Arg Glu Thr 115 120 125

Thr Gln Leu Pro Thr Thr His Gln Ala Ser Thr Thr Thr Ala Thr Thr 130  $$135\$ 

Ala Gln Glu Pro Ala Thr Ser His Pro His Arg Asp Met Gln Pro Gly 145 150 155 160

His His Glu Thr Ser Thr Pro Ala Gly Pro Ser Gln Ala Asp Leu His 165 170 175

Thr Pro His Thr Glu Asp Gly Gly Pro Ser Ala Thr Glu Arg Ala Ala 180  $$185\$ 

Glu Asp Gly Ala Ser Ser Gln Leu Pro Ala Ala Glu Gly Ser Gly Glu 195 200 205

Gln Asp Phe Thr Phe Glu Thr Ser Gly Glu Asn Thr Ala Val Val Ala 210 215 220

Val Glu Pro Asp Arg Arg Asn Gln Ser Pro Val Asp Gln Gly Ala Thr 225 230 235 240

Gly Ala Ser Gln Gly Leu Leu Asp Arg Lys Glu Val Leu Gly Gly Val 255

Ile Ala Gly Gly Leu Val Gly Leu Ile Phe Ala Val Cys Leu Val Gly 260 265 270

Phe Met Leu Tyr Arg Met Lys Lys Lys Asp Glu Gly Ser Tyr Ser Leu 275 280 285

Glu Glu Pro Lys Gln Ala Asn Gly Gly Ala Tyr Gln Lys Pro Thr Lys 290 295 300

Gln Glu Glu Phe Tyr Ala 305 310

<210>

<211> 2174 <212> PRT

<213> Homo sapiens

<400> 126

Met Ser Ala Ser Phe Val Pro Asn Gly Ala Ser Leu Glu Asp Cys His 1  $\phantom{\Big|}$  5  $\phantom{\Big|}$  10  $\phantom{\Big|}$  15

Cys Asn Leu Phe Cys Leu Ala Asp Leu Thr Gly Ile Lys Trp Lys Lys 20 25 30

Tyr Val Trp Gln Gly Pro Thr Ser Ala Pro Ile Leu Phe Pro Val Thr 35 40 45

Glu Glu Asp Pro Ile Leu Ser Ser Phe Ser Arg Cys Leu Lys Ala Asp 50 55

Val Leu Gly Val Trp Arg Arg Asp Gln Arg Pro Gly Arg Arg Glu Leu 65 70 75 80

Trp Ile Phe Trp Gly Glu Asp Pro Val Leu Leu Thr Leu Phe Thr 85 90 95

Met Thr Tyr Gln Lys Lys Met Glu Cys Gly Arg Met Asp Phe Pro 100 105 110

Met Asn Ala Val Leu Cys Phe Ser Lys Ala Val His Asn Leu Leu Glu 115 120 125

Arg Cys Leu Met Asn Arg Asn Phe Val Arg Ile Gly Lys Trp Phe Val

Lys Pro Tyr Glu Lys Asp Glu Lys Pro Ile Asn Lys Ser Glu His Leu 145 150 155 160

Ser Cys Ser Phe Thr Phe Phe Leu His Gly Asp Ser Asn Val Cys Thr

Ser Val Glu Ile Asn Gln His Gln Pro Val Tyr Leu Leu Ser Glu Glu  $180^{\circ}$  185 190

His Ile Thr Leu Ala Gln Gln Ser Asn Ser Pro Phe Gln Val Ile Leu 195 200 205

Cys Pro Phe Gly Leu Asn Gly Thr Leu Thr Gly Gln Ala Phe Lys Met 210 225 220

Ser Asp Ser Ala Thr Lys Lys Leu Ile Gly Glu Trp Lys Gln Phe Tyr 225 230 235 240

Pro Ile Ser Cys Cys Leu Lys Glu Met Ser Glu Glu Lys Gln Glu Asp 245 250 255

Met Asp Trp Glu Asp Asp Ser Leu Ala Ala Val Glu Val Leu Val Ala 260 265 270

Gly Val Arg Met Ile Tyr Pro Ala Cys Phe Val Leu Val Pro Gln Ser 275 280 285

Asp Ile Pro Thr Pro Ser Pro Val Gly Ser Thr His Cys Ser Ser Ser 290 300

Cys Leu Gly Val His Gln Val Pro Ala Ser Thr Arg Asp Pro Ala Met 305 310 315 320

Ser Ser Val Thr Leu Thr Pro Pro Thr Ser Pro Glu Glu Val Gln Thr 325  $^{\circ}$  330  $^{\circ}$  335

Val Asp Pro Gln Ser Val Gln Lys Trp Val Lys Phe Ser Ser Val Ser 340 345 350

Asp Gly Phe Asn Ser Asp Ser Thr Ser His His Gly Gly Lys Ile Pro 355 360 365

Arg Lys Leu Ala Asn His Val Val Asp Arg Val Trp Gln Glu Cys Asn 370 380

Met Asn Arg Ala Gln Asn Lys Lys Lys Tyr Ser Ala Ser Ser Gly Gly 385 390 395 400

Leu Cys Glu Glu Ala Thr Ala Ala Lys Val Ala Ser Trp Asp Phe Val 405 410 415

Glu Ala Thr Gln Arg Thr Asn Cys Ser Cys Leu Arg His Lys Asn Leu 420 425 430

Lys Ser Arg Asn Ala Gly Gln Gln Gly Gln Ala Pro Ser Leu Gly Gln 435  $\phantom{\bigg|}445\phantom{\bigg|}$ 

Gln Gln Gln Ile Leu Pro Lys His Lys Thr Asn Glu Lys Gln Glu Lys 450 455 460

Ser Glu Glu Pro Gln Lys Arg Pro Leu Thr Pro Phe His His Arg Val 465 470 475 480

Ser Val Ser Asp Asp Val Gly Met Asp Ala Asp Ser Ala Ser Gln Arg 485 490 495

Leu Val Ile Ser Ala Pro Asp Ser Gln Val Arg Phe Ser Asn Ile Arg  $500 \hspace{1.5cm} 505 \hspace{1.5cm} 510$ 

Thr Asn Asp Val Ala Lys Thr Pro Gln Met His Gly Thr Glu Met Ala 515 520 525

Asn Ser Pro Gln Pro Pro Pro Leu Ser Pro His Pro Cys Asp Val Val 530 535 540

Asp Glu Gly Val Thr Lys Thr Pro Ser Thr Pro Gln Ser Gln His Phe 545 550 560

Tyr Gln Met Pro Thr Pro Asp Pro Leu Val Pro Ser Lys Pro Met Glu 565 570 575

Asp Arg Ile Asp Ser Leu Ser Gln Ser Phe Pro Pro Gln Tyr Gln Glu 580 585 590

Ala Val Glu Pro Thr Val Tyr Val Gly Thr Ala Val Asn Leu Glu Glu 595  $\phantom{\bigg|}$  600  $\phantom{\bigg|}$  605

Asp Glu Ala Asn Ile Ala Trp Lys Tyr Tyr Lys Phe Pro Lys Lys Lys 610 615 620

Asp Val Glu Phe Leu Pro Pro Gln Leu Pro Ser Asp Lys Phe Lys Asp 625 630 635 640

Asp Pro Val Gly Pro Phe Gly Gln Glu Ser Val Thr Ser Val Thr Glu 645 650 655

Leu Met Val Gln Cys Lys Lys Pro Leu Lys Val Ser Asp Glu Leu Val 660 665 670

Gln Gln Tyr Gln Ile Lys Asn Gln Cys Leu Ser Ala Ile Ala Ser Asp 675 680 685

Ala Glu Gln Glu Pro Lys Ile Asp Pro Tyr Ala Phe Val Glu Gly Asp 690 695 700

Glu Glu Phe Leu Phe Pro Asp Lys Lys Asp Arg Gln Asn Ser Glu Arg 705 710 715 720

Glu Ala Gly Lys Lys His Lys Val Glu Asp Gly Thr Ser Ser Val Thr 725  $\phantom{000}730$   $\phantom{000}735$ 

Val Leu Ser His Glu Glu Asp Ala Met Ser Leu Phe Ser Pro Ser Ile 740 745 750

Lys Gln Asp Ala Pro Arg Pro Thr Ser His Ala Arg Pro Pro Ser Thr 755 760 765

Ser Leu Ile Tyr Asp Ser Asp Leu Ala Val Ser Tyr Thr Asp Leu Asp 770 780

Asn Leu Phe Asn Ser Asp Glu Asp Glu Leu Thr Pro Gly Ser Lys Arg 785 790 795 800

Ser Ala Asn Gly Ser Asp Asp Lys Ala Ser Cys Lys Glu Ser Lys Thr 805 810 815

Gly Asn Leu Asp Pro Leu Ser Cys Ile Ser Thr Ala Asp Leu His Lys 820 825 830

Met Tyr Pro Thr Pro Pro Ser Leu Glu Gln His Ile Met Gly Phe Ser 835 840 845

Pro Met Asn Met Asn Asn Lys Glu Tyr Gly Ser Met Asp Thr Thr Pro 850  $\,$  860

Gly Gly Thr Val Leu Glu Gly Asn Ser Ser Ser Ile Gly Ala Gln Phe 865 870 875 880

Lys Ile Glu Val Asp Glu Gly Phe Cys Ser Pro Lys Pro Ser Glu Ile 885 890 895

Lys Asp Phe Ser Tyr Val Tyr Lys Pro Glu Asn Cys Gln Ile Leu Val  $900 \hspace{1.5cm} 905 \hspace{1.5cm} 910$ 

Gly Cys Ser Met Phe Ala Pro Leu Lys Thr Leu Pro Ser Gln Tyr Leu 915 920 925

Pro Leu Ile Lys Leu Pro Glu Glu Cys Ile Tyr Arg Gln Ser Trp Thr 930 935 940

Val Gly Lys Leu Glu Leu Leu Ser Ser Gly Pro Ser Met Pro Phe Ile 945 950 955 960

Lys Glu Gly Asp Gly Ser Asn Met Asp Gln Glu Tyr Gly Thr Ala Tyr 965 970 970 975

Thr Pro Gln Thr His Thr Ser Cys Gly Met Pro Pro Ser Ser Ala Pro 980 985 990

Pro Ser Asn Ser Gly Ala Gly Ile Leu Pro Ser Pro Ser Thr Pro Arg 995 1000 1005

Phe Pro Thr Pro Arg Thr Pro Arg Thr Pro Arg Thr Pro Arg Gly 1010 1015 1020

Ala Gly Gly Pro Ala Ser Ala Gln Gly Ser Val Lys Tyr Glu Asn 1025 1030 1035

Ser Asp Leu Tyr Ser Pro Ala Ser Thr Pro Ser Thr Cys Arg Pro 1040  $1040\,$ 

Leu Asn Ser Val Glu Pro Ala Thr Val Pro Ser Ile Pro Glu Ala 1055 1060 1065

His Ser Leu Tyr Val Asn Leu Ile Leu Ser Glu Ser Val Met Asn 1070 1075 1080

Leu Phe Lys Asp Cys Asn Ser Asp Ser Cys Cys Ile Cys Val Cys 1085 1095 1095

Asn Met Asn Ile Lys Gly Ala Asp Val Gly Val Tyr Ile Pro Asp Page 183

1110

Pro Th	r Gln	Glu A	Ala G	ln :	Tyr	Arg	Cys	Thr	Cys	Gly	Phe	Ser	Ala
						-	-		-				

1105

1100

1113

Val Met Asn Arg Lys Phe Gly Asn Asn Ser Gly Leu Phe Leu Glu 1130 1140

Asp Glu Leu Asp Ile Ile Gly Arg Asn Thr Asp Cys Gly Lys Glu 1145 1150 1155

Ala Glu Lys Arg Phe Glu Ala Leu Arg Ala Thr Ser Ala Glu His 1160  $\,$  1170

Val Asn Gly Gly Leu Lys Glu Ser Glu Lys Leu Ser Asp Asp Leu 1175 1180 1185

Ile Leu Leu Gln Asp Gln Cys Thr Asn Leu Phe Ser Pro Phe 1190 1195 1200

Asn Trp Val Arg Val Glu Glu Arg Asp Cys Cys Asn Asp Cys Tyr 1220 1225

Leu Ala Leu Glu His Gly Arg Gln Phe Met Asp Asn Met Ser Gly 1235 1240 1245

Gly Lys Val Asp Glu Ala Leu Val Lys Ser Ser Cys Leu His Pro  $1250 \hspace{1.5cm} 1260$ 

Trp Ser Lys Arg Asn Asp Val Ser Met Gln Cys Ser Gln Asp Ile 1265 1270 1275

Leu Arg Met Leu Leu Ser Leu Gln Pro Val Leu Gln Asp Ala Ile 1280 1285 1290

Gln Lys Lys Arg Thr Val Arg Pro Trp Gly Val Gln Gly Pro Leu 1295 1300 1305

Thr Trp Gln Gln Phe His Lys Met Ala Gly Arg Gly Ser Tyr Gly 1310 1315 1320

Thr Asp Glu Ser Pro Glu Pro Leu Pro Ile Pro Thr Phe Leu Leu 1325 1330 1335

Gly Tyr Asp Tyr Asp Tyr Leu Val Leu Ser Pro Phe Ala Leu Pro 1340 1350

Tyr Trp Glu Arg Leu Met Leu Glu Pro Tyr Gly Ser Gln Arg Asp 1355 1360 1365

Ile Ala Tyr Val Val Leu Cys Pro Glu Asn Glu Ala Leu Leu Asn 1370 1375 1380

Gly Ala Lys Ser Phe Phe Arg Asp Leu Thr Ala Ile Tyr Glu Ser 1385 1390 1395

Cys	Arg 1400		Gly	Gln		Arg 1405		Val	Ser	Arg	Leu 1410		Thr	Asp
Gly	Ile 1415	Met	Arg	Val	Gly	Ser 1420	Thr	Ala	Ser	Lys	Lys 1425		Ser	Glu
Lys	Leu 1430	Val	Ala	Glu	Trp	Phe 1435	Ser	Ģln	Ala	Ala	Asp 1440	Gly	Asn	Asn
Glu	Ala 1445	Phe	Ser	Lys	Leu	Lys 1450	Leu	Tyr	Ala	Gln	Val 1455	Cys	Arg	Tyr
Asp	Leu 1460	Gly	Pro	Tyr	Leu	Ala 1465	Ser	Leu	Pro	Leu	Asp 1470		Ser	Leu
Leu	Ser 1475	Gln	Pro	Asn	Leu	Val 1480	Ala	Pro	Thr	Ser	Gln 1485	Ser	Leu	Ile
Thr	Pro 1490		Gln	Met	Thr	Asn 1495		Gly	Asn	Ala	Asn 1500	Thr	Pro	Ser
Ala	Thr 1505		Ala	Ser	Ala	Ala 1510		Ser	Thr	Met	Thr 1515		Thr	Ser
Gly	Val 1520	Ala	Ile	Ser	Thr	Ser 1525	Val	Ala	Thr	Ala	Asn 1530	Ser	Thr	Leu
Thr	Thr 1535	Ala	Ser	Thr	Ser	Ser 1540		Ser	Ser	Ser	Asn 1545	Leu	Asn	Ser
Gly	Val 1550	Ser	Ser	Asn		Leu 1555	Pro	Ser	Phe	Pro	Pro 1560	Phe	Gly	Ser
Met	Asn 1565		Asn	Ala		Gly 1570		Met	Ser		Gln 1575		Asn	Thr
Val	Gln 1580		Gly	Gln	Leu	Gly 1585		Gln	Gln	Thr	Ser 1590	Ala	Leu	Gln
Thr	Ala 1595	Gly	Ile	Ser	Gly	Glu 1600	Ser	Ser	Ser	Leu	Pro 1605	Thr	Gln	Pro
His	Pro 1610	Asp	Val	Ser	Glu	Ser 1615	Thr	Met	Asp	Arg	Asp 1620	Lys	Val _	Gly
Ile	Pro 1625	Thr	Asp	Gly	Asp	Ser 1630	His	Ala	Val	Thr	Туг 1635	Pro	Pro	Ala
Ile	Val 1640	Val	Tyr	Ile	Ile	Asp 1645	Pro	Phe	Thr	Tyr	Glu 1650	Asn	Thr	Asp
Glu	Ser 1655	Thr	Asn	Ser	Ser	Ser 1660	Val	Trp	Thr	Leu	Gly 1665	Leu	Leu	Arg
Cys	Phe 1670	Leu	Glu	Met	Val	Gln 1675	Thr	Leu	Pro	Pro	His 1680	Ile	Lys	Ser

Thr Val Ser Val Gln Ile Ile Pro Cys Gln Tyr Leu Leu Gln Pro 1685 1690 1695

Val	Lys 1700	His	Glu	Asp	Arg	Glu 1705	Ile	Tyr	Pro	Gln	His 1710	Leu	Lys	Ser
	Ala 1715	Phe	Ser	Ala	Phe	Thr 1720	Gln	Суз	Arg	Arg	Pro 1725	Leu	Pro	Thr
Ser	Thr 1730	Asn	Val	Lys	Thr	Leu 1735	Thr	Gly	Phe	Gly	Pro 1740	Gly	Leu	Ala
Met	Glu 1745	Thr	Ala	Leu	Arg	Ser 1750	Pro	Asp	Arg	Pro	Glu 1755	Cys	Ile	Arg
Leu	Tyr 1760	Ala	Pro	Pro	Phe	Ile 1765	Leu	Ala	Pro		Lys 1770		Lys	Gln
Thr	Glu 1775	Leu	Gly	Glu	Thr	Phe 1780	Gly	Glu	Ala	Gly	Gln 1785	Lys	Tyr	Asn
Vál	Leu 1790		Val	Gly		Cys 1795		Ser	His		Gln 1800	Arg	Trp	Ile
Leu	Ala 1805		Cys	Thr	Asp	Leu 1810		Gly	Glu	Leu	Leu 1815	Glu	Thr	Cys
Ile	Ile 1820		Ile	Asp	Val	Pro 1825		Arg	Ala	Arg	Arg 1830		Lys	Ser
Ser	Ala 1835	Arg	Lys	Phe	Gly	Leu 1840	Gln	Lys	Leu	Trp	Glu 1845		Cys	Leu
Gly	Leu 1850		Gln	Met	Ser	Ser 1855	Leu	Pro	Trp	Arg	Val 1860	Val	Ile	Gly
Arg	Leu 1865	Gly	Arg	Ile	Gly	His 1870		Glu	Leu	Lys	Asp 1875		Ser	Cys
Leu	Leu 1880		Arg	Arg	Asn	Leu 1885		Ser	Leu	Ser	Lys 1890		Leu	Lys
Asp	Met 1895	Суз	Arg	Met	Cys	Gly 1900	Ile	Ser	Ala	Ala	Asp 1905	Ser	Pro	Ser
Ile	Leu 1910	Ser	Ala	Суз	Leu	Val 1915		Met	Glu	Pro	Gln 1920	Gly	Ser	Phe
Val	Ile 1925	Met	Pro	Asp	Ser	Val 1930	Ser	Thr	Gly	Ser	Val 1935		Gly	Arg
Ser	Thr 1940		Leu	Asn	Met	Gln 1945		Ser	Gln	Leu	Asn 1950		Pro	Gln
Asp	Thr 1955	Ser	Cys	Thr	His	Ile 1960		Val	Phe	Pro	Thr 1965		Ala	Ser
Val	Gln 1970		Ala	Ser	Ala	Thr 1975		Thr	Thr	Glu	Asn 1980		Asp	Leu
Ala	Phe 1985	Asn	Pro	Asn	Asn	Asp 1990		Ala	Asp	_	Met 1995 ge 18		Ile	Phe

Asp Leu Leu Asp Thr Gly Asp Asp Leu Asp Pro Asp Ile Ile Asn 2000 2005

Ile Leu Pro Ala Ser Pro Thr Gly Ser Pro Val His Ser Pro Gly 2015 2020

Ser His Tyr Pro His Gly Gly Asp Ala Gly Lys Gly Gln Ser Thr 2030 2040

Asp Arg Leu Leu Ser Thr Glu Pro His Glu Glu Val Pro Asn Ile 2045 2055

Leu Gln Gln Pro Leu Ala Leu Gly Tyr Phe Val Ser Thr Ala Lys 2060 2065 2070

Ala Gly Pro Leu Pro Asp Trp Phe Trp Ser Ala Cys Pro Gln Ala 2075  $\phantom{\bigg|}$  2080  $\phantom{\bigg|}$  2080  $\phantom{\bigg|}$  2085  $\phantom{\bigg|}$ 

Gln Tyr Gln Cys Pro Leu Phe Leu Lys Ala Ser Leu His Leu His 2090 2095 2100

Val Pro Ser Val Gln Ser Asp Glu Leu Leu His Ser Lys His Ser 2105 2110 2115

His Pro Leu Asp Ser Asn Gln Thr Ser Asp Val Leu Arg Phe Val 2120 2125 2130

Leu Glu Gln Tyr Asn Ala Leu Ser Trp Leu Thr Cys Asp Pro Ala 2135 2140 2145

Thr Gln Asp Arg Arg Ser Cys Leu Pro Ile His Phe Val Val Leu 2150 2155 2160

Asn Gln Leu Tyr Asn Phe Ile Met Asn Met Leu 2165 2170

<210> 127 <211> 415

<211> 415 <212> PRT

<213> Homo sapiens

<400> .127

Met Glu Leu Arg Val Gly Asn Arg Tyr Arg Leu Gly Arg Lys Ile Gly 1 5 10 15

Ser Gly Ser Phe Gly Asp Ile Tyr Leu Gly Thr Asp Ile Ala Ala Gly 20 25 30

Glu Glu Val Ala Ile Lys Leu Glu Cys Val Lys Thr Lys His Pro Gln  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Leu His Ile Glu Ser Lys Ile Tyr Lys Met Met Gln Gly Gly Val Gly 50  $\,$ 

Ile Pro Thr Ile Arg Trp Cys Gly Ala Glu Gly Asp Tyr Asn Val Met 65 70 75 80

Val Met Glu Leu Leu Gly Pro Ser Leu Glu Asp Leu Phe Asn Phe Cys 85 90 95

Ser Arg Lys Phe Ser Leu Lys Thr Val Leu Leu Leu Ala Asp Gln Met 100 105 110Ile Ser Arg Ile Glu Tyr Ile His Ser Lys Asn Phe Ile His Arg Asp 115 120 125 Val Lys Pro Asp Asn Phe Leu Met Gly Leu Gly Lys Lys Gly Asn Leu 130 140 Val Tyr Ile Ile Asp Phe Gly Leu Ala Lys Lys Tyr Arg Asp Ala Arg 145 150 155 160 Thr His Gln His Ile Pro Tyr Arg Glu Asn Lys Asn Leu Thr Gly Thr 165 170 175Ala Arg Tyr Ala Ser Ile Asn Thr His Leu Gly Ile Glu Gln Ser Arg  $180 \\ \hspace*{1.5cm} 185 \\ \hspace*{1.5cm} 190 \\ \hspace*{1.5cm}$ Arg Asp Asp Leu Glu Ser Leu Gly Tyr Val Leu Met Tyr Phe Asn Leu 195 200 205 Gly Ser Leu Pro Trp Gln Gly Leu Lys Ala Ala Thr Lys Arg Gln Lys 210 215 220 Tyr Glu Arg Ile Ser Glu Lys Lys Met Ser Thr Pro Ile Glu Val Leu 225 230 240 Cys Lys Gly Tyr Pro Ser Glu Phe Ala Thr Tyr Leu Asn Phe Cys Arg 245 250 255 Ser Leu Arg Phe Asp Asp Lys Pro Asp Tyr Ser Tyr Leu Arg Gln Leu 260 265 270Phe Arg Asn Leu Phe His Arg Gln Gly Phe Ser Tyr Asp Tyr Val Phe 275 280 285 Asp Trp Asn Met Leu Lys Phe Gly Ala Ser Arg Ala Ala Asp Asp Ala 290 295 300 Glu Arg Glu Arg Arg Asp Arg Glu Glu Arg Leu Arg His Ser Arg Asn 305 310 315 320 Pro Ala Thr Arg Gly Leu Pro Ser Thr Asp Ser Gly Arg Leu Arg Gly 325 330 335 Thr Gln Glu Val Ala Pro Pro Thr Pro Leu Thr Pro Thr Ser His Thr 340 345 350Ala Asn Thr Ser Pro Arg Pro Val Ser Gly Met Glu Arg Glu Arg Lys 355 360 365Val Ser Met Arg Leu His Arg Gly Ala Pro Val Asn Ile Ser Ser Ser 370 380 Asp Leu Thr Gly Arg Gln Asp Thr Ser Arg Met Ser Thr Ser Gln Ile 385 390 395 400 Pro Gly Arg Val Ala Ser Ser Gly Leu Gln Ser Val Val His Arg Page 188

405 410 415

<210> 128

<211> 204

<212> PRT

<213> Homo sapiens

<400> 128

Met Thr Glu Trp Glu Thr Ala Ala Pro Ala Val Ala Glu Thr Pro Asp 1 10 15

Ile Lys Leu Phe Gly Lys Trp Ser Thr Asp Asp Val Gln Ile Asn Asp 20 25 30

Ile Ser Leu Gln Asp Tyr Ile Ala Val Lys Glu Lys Tyr Ala Lys Tyr 35 40 45

Leu Pro His Ser Ala Gly Arg Tyr Ala Ala Asn Ala Phe Arg Lys Ala 50 60

Gln Cys Pro Ile Val Glu Arg Leu Thr Asn Ser Met Met His Gly 65 70 75 80

Arg Asn Asn Gly Lys Lys Leu Met Thr Val Arg Ile Val Lys His Ala 85 90 95

Phe Glu Ile Ile His Leu Leu Thr Gly Glu Asn Pro Leu Gln Val Leu 100 105 110

Val Asn Ala Ile Ile Asn Ser Gly Pro Arg Glu Asp Ser Thr Arg Ile 115 120 125

Gly Arg Ala Gly Thr Val Arg Arg Gln Ala Val Asp Val Ser Pro Leu 130 135 140

Arg Arg Val Asn Gln Ala Ile Trp Leu Leu Cys Thr Gly Ala Arg Glu 145  $\phantom{\bigg|}$  150  $\phantom{\bigg|}$  150  $\phantom{\bigg|}$  155  $\phantom{\bigg|}$  160

Ala Ala Phe Arg Asn Ile Lys Thr Ile Ala Glu Cys Leu Ala Asp Glu 165 170 175

Leu Ile Asn Ala Ala Lys Gly Ser Ser Asn Ser Tyr Ala Ile Lys Lys 180 185 190

Lys Asp Glu Leu Glu Arg Val Ala Lys Ser Asn Arg 195 200

<210> 129

<211> 694

<212> PRT

<213> Homo sapiens

<400> 129

Met Glu Asn Lys Ser Leu Glu Ser Ser Gln Thr Asp Leu Lys Leu Val 1  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Ala His Pro Arg Ala Lys Ser Lys Val Trp Lys Tyr Phe Gly Phe Asp  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Thr Asn Ala Glu Gly Cys Ile Leu Gln Trp Lys Lys Ile Tyr Cys Arg  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Ile Cys Met Ala Gln Ile Ala Tyr Ser Gly Asn Thr Ser Asn Leu Ser 50 60Tyr His Leu Glu Lys Asn His Pro Glu Glu Phe Cys Glu Phe Val Lys 65 70 75 80 Ser Asn Thr Glu Gln Met Arg Glu Ala Phe Ala Thr Ala Phe Ser Lys 85 90 95 Leu Lys Pro Glu Ser Ser Gln Gln Pro Gly Gln Asp Ala Leu Ala Val 100 105 110Lys Ala Gly His Gly Tyr Asp Ser Lys Lys Gln Gln Glu Leu Thr Ala 115 120 125Ala Val Leu Gly Leu Ile Cys Glu Gly Leu Tyr Pro Ala Ser Ile Val 130 135 140 Asp Glu Pro Thr Phe Lys Val Leu Leu Lys Thr Ala Asp Pro Arg Tyr 145 150 150 155 160 Glu Leu Pro Ser Arg Lys Tyr Ile Ser Thr Lys Ala Ile Pro Glu Lys 165 170 175Tyr Gly Ala Val Arg Glu Val Ile Leu Lys Glu Leu Ala Glu Ala Thr  $180 \,\,\,$ Trp Cys Gly Ile Ser Thr Asp Met Trp Arg Ser Glu Asn Gln Asn Arg 195 200 205 Ala Tyr Val Thr Leu Ala Ala His Phe Leu Gly Leu Gly Ala Pro Asn 210 215 220Cys Leu Ser Met Gly Ser Arg Cys Leu Lys Thr Phe Glu Val Pro Glu 225 230 235 240 Glu Asn Thr Ala Glu Thr Ile Thr Arg Val Leu Tyr Glu Val Phe Ile 245 250 255 Glu Trp Gly Ile Ser Ala Lys Val Phe Gly Ala Thr Thr Asn Tyr Gly 260 265 270Lys Asp Ile Val Lys Ala Cys Ser Leu Leu Asp Val Ala Val His Met 275 280 285 Pro Cys Leu Gly His Thr Phe Asn Ala Gly Ile Gln Gln Ala Phe Gln 290 300 Leu Pro Lys Leu Gly Ala Leu Leu Ser Arg Cys Arg Lys Leu Val Glu 305 310 315 320 Tyr Phe Gln Gln Ser Ala Val Ala Met Tyr Met Leu Tyr Glu Lys Gln 325 330 335 Lys Gln Gln Asn Val Ala His Cys Met Leu Val Ser Asn Arg Val Ser 340 345 350Trp Trp Gly Ser Thr Leu Ala Met Leu Gln Arg Leu Lys Glu Gln Gln Page 190

355 360 34

Phe Val Ile Ala Gly Val Leu Val Glu Asp Ser Asn Asn His His Leu 370 375 380

Met Leu Glu Ala Ser Glu Trp Ala Thr Ile Glu Gly Leu Val Glu Leu 385 390 395 400

Leu Gln Pro Phe Lys Gln Val Ala Glu Met Leu Ser Ala Ser Arg Tyr 405 410 415

Pro Thr Ile Ser Met Val Lys Pro Leu Leu His Met Leu Leu Asn Thr 420 425 430

Thr Leu Asn Ile Lys Glu Thr Asp Ser Lys Glu Leu Ser Met Ala Lys  $435 \hspace{1.5cm} 440 \hspace{1.5cm} 445$ 

Glu Val Ile Ala Lys Glu Leu Ser Lys Thr Tyr Gln Glu Thr Pro Glu 450  $\phantom{\bigg|}455\phantom{\bigg|}50\phantom{\bigg|}460\phantom{\bigg|}$ 

Ile Asp Met Phe Leu Asn Val Ala Thr Phe Leu Asp Pro Arg Tyr Lys 465 470 475 480

Arg Leu Pro Phe Leu Ser Ala Phe Glu Arg Gln Gln Val Glu Asn Arg 485 490 495

Val Val Glu Glu Ala Lys Gly Leu Leu Asp Lys Val Lys Asp Gly Gly 500 505 510

Tyr Arg Pro Ala Glu Asp Lys Ile Phe Pro Val Pro Glu Glu Pro Pro 515 520 525

Val Lys Lys Leu Met Arg Thr Ser Thr Pro Pro Pro Ala Ser Val Ile 530 540

Asn Asn Met Leu Ala Glu Ile Phe Cys Gln Thr Gly Gly Val Glu Asp 545 550 555 560

Gln Glu Glu Trp His Ala Gln Val Val Glu Glu Leu Ser Asn Phe Lys 565 570 575

Ser Gln Lys Val Leu Gly Leu Asn Glu Asp Pro Leu Lys Trp Trp Ser 580 585 590

Asp Arg Leu Ala Leu Phe Pro Leu Leu Pro Lys Val Leu Gin Lys Tyr 595 600 605

Trp Cys Val Thr Ala Thr Arg Val Ala Pro Glu Arg Leu Phe Gly Ser 610 615 620

Ala Ala Asn Val Val Ser Ala Lys Arg Asn Arg Leu Ala Pro Ala His 625 630 635 640

Val Asp Glu Gln Val Phe Leu Tyr Glu Asn Ala Arg Ser Gly Ala Glu 645 650 655

Ala Glu Pro Glu Asp Gln Asp Glu Gly Glu Trp Gly Leu Asp Gln Glu 660 665 670

Gln Val Phe Ser Leu Gly Asp Gly Val Ser Gly Gly Fine Fine Gly 11e 675 680 685

Arg Asp Ser Ser Phe Leu 690

<210> 130

<211> 729 <212> PRT

<213> Homo sapiens

<400> 130

Met Gly Lys Lys Tyr Lys Asn Ile Val Leu Leu Lys Gly Leu Glu Val 1 5 5 10 10 15

Ile Asn Asp Tyr His Phe Arg Met Val Lys Ser Leu Leu Ser Asn Asp 20 25 30

Leu Lys Leu Asn Leu Lys Met Arg Glu Glu Tyr Asp Lys Ile Gln Ile  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Ala Asp Leu Met Glu Glu Lys Phe Arg Gly Asp Ala Gly Leu Gly Lys 50 60

Leu Ile Lys Ile Phe Glu Asp Ile Pro Thr Leu Glu Asp Leu Ala Glu 65 70 75 80

Thr Leu Lys Lys Glu Lys Leu Lys Val Lys Gly Pro Ala Leu Ser Arg 85 90 95

Lys Arg Lys Glu Val His Ala Thr Ser Pro Ala Pro Ser Thr Ser 100 \$105\$

Ser Thr Val Lys Thr Glu Gly Ala Glu Ala Thr Pro Gly Ala Gln Lys 115 120 125

Arg Lys Lys Ser Thr Lys Glu Lys Ala Gly Pro Lys Gly Ser Lys Val

Ser Glu Glu Gln Thr Gln Pro Pro Ser Pro Ala Gly Ala Gly Met Ser 145 150 150 155 160

Thr Ala Met Gly Arg Ser Pro Ser Pro Lys Thr Ser Leu Ser Ala Pro 165 170 175

Pro Asn Ser Ser Ser Thr Glu Asn Pro Lys Thr Val Ala Lys Cys Gln 180 185 190

Val Thr Pro Arg Arg Asn Val Leu Gln Lys Arg Pro Val Ile Val Lys 195 200 205

Val Leu Ser Thr Thr Lys Pro Phe Glu Tyr Glu Thr Pro Glu Met Glu 210 215 220

Lys Lys Ile Met Phe His Ala Thr Val Ala Thr Gln Thr Gln Phe Phe 225 230 235 240

His Val Lys Val Leu Asn Thr Ser Leu Lys Glu Lys Phe Asn Gly Lys 245 250 255

- Lys Ile Ile Ile Ser Asp Tyr Leu Giu Tyr Asp Ser Leu Leu Giu 260 265 270
- Val Asn Glu Glu Ser Thr Val Ser Glu Ala Gly Pro Asn Gln Thr Phe 275 280 285
- Glu Val Pro Asn Lys Ile Ile Asn Arg Ala Lys Glu Thr Leu Lys Ile 290 295 300
- Asp Ile Leu His Lys Gln Ala Ser Gly Asn Ile Val Tyr Gly Val Phe 305 310 315 320
- Met Leu His Lys Lys Thr Val Asn Gln Lys Thr Thr Ile Tyr Glu Ile 325 330 335
- Gln Asp Asp Arg Gly Lys Met Asp Val Val Gly Thr Gly Gln Cys His  $340 \hspace{1.5cm} 345 \hspace{1.5cm} 350$
- Asn Ile Pro Cys Glu Glu Gly Asp Lys Leu Gln Leu Phe Cys Phe Arg  $355 \hspace{1cm} 360 \hspace{1cm} 365$
- Leu Arg Lys Lys Asn Gln Met Ser Lys Leu Ile Ser Glu Met His Ser 370 380
- Phe Ile Gln Ile Lys Lys Lys Thr Asn Pro Arg Asn Asn Asp Pro Lys 385 390 395 400
- Ser Met Lys Leu Pro Gln Glu Gln Arg Gln Leu Pro Tyr Pro Ser Glu 405 410 415
- Ala Ser Thr Thr Phe Pro Glu Ser His Leu Arg Thr Pro Gln Met Pro 420 425 430
- Pro Thr Thr Pro Ser Ser Ser Phe Phe Thr Lys Lys Ser Glu Asp Thr 435 440 445
- Ile Ser Lys Met Asn Asp Phe Met Arg Met Gln Ile Leu Lys Glu Gly 450 455 460
- Ser His Phe Pro Gly Pro Phe Met Thr Ser Ile Gly Pro Ala Glu Ser 465 470 475 480
- His Pro His Thr Pro Gln Met Pro Pro Ser Thr Pro Ser Ser Ser Phe 485 490 495
- Leu Thr Thr Leu Lys Pro Arg Leu Lys Thr Glu Pro Glu Glu Val Ser 500 505 510
- Ile Glu Asp Ser Ala Gln Ser Asp Leu Lys Glu Val Met Val Leu Asn 515 525 525
- Ala Thr Glu Ser Phe Val Tyr Glu Pro Lys Glu Gln Lys Lys Met Phe 530 540
- His Ala Thr Val Ala Thr Glu Asn Glu Val Phe Arg Val Lys Val Phe 545 550 560
- Asn Ile Asp Leu Lys Glu Lys Phe Thr Pro Lys Lys Ile Ile Ala Ile 565 570 575

Ala Asn Tyr Val Cys Arg Asn Gly Phe Leu Glu Val Tyr Pro Phe Thr 580 . 585 585

Leu Val Ala Asp Val Asn Ala Asp Arg Asn Met Glu Ile Pro Lys Gly 595 600 605

Leu Ile Arg Ser Ala Ser Val Thr Pro Lys Ile Asn Gln Leu Cys Ser 610 615 620

Gln Thr Lys Gly Ser Phe Val Asn Gly Val Phe Glu Val His Lys Lys 625 630 635 640

Asn Val Arg Gly Glu Phe Thr Tyr Tyr Glu Ile Gln Asp Asn Thr Gly 645 650 655

Lys Met Glu Val Val Val His Gly Arg Leu Asn Thr Ile Asn Cys Glu  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670 \hspace{1.5cm}$ 

Glu Gly Asp Lys Leu Lys Leu Thr Ser Phe Glu Leu Ala Pro Lys Ser 675  $\,$  680  $\,$  685

Gly Asn Thr Gly Glu Leu Arg Ser Val Ile His Ser His Ile Lys Val  $690 \hspace{1.5cm} 695 \hspace{1.5cm} 700$ 

Ile Lys Thr Arg Lys Asn Lys Lys Asp Ile Leu Asn Pro Asp Ser Ser 705 710 715 720

Met Glu Thr Ser Pro Asp Phe Phe Phe 725

<210>

<211> 216

<212> PRT

<213> Homo sapiens

<400> 131

Met Leu Arg Leu Ser Glu Arg Asn Met Lys Val Leu Leu Ala Ala Ala 1 5 10 15

Leu Ile Ala Gly Ser Val Phe Phe Leu Leu Leu Pro Gly Pro Ser Ala 20 25 30

Ala Asp Glu Lys Lys Lys Gly Pro Lys Val Thr Val Lys Val Tyr Phe  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Asp Leu Arg Ile Gly Asp Glu Asp Val Gly Arg Val Ile Phe Gly Leu 50 60

Phe Gly Lys Thr Val Pro Lys Thr Val Asp Asn Phe Val Ala Leu Ala 65 70 75 80

Thr Gly Glu Lys Gly Phe Gly Tyr Lys Asn Ser Lys Phe His Arg Val 85 90 95

Ile Lys Asp Phe Met Ile Gln Gly Gly Asp Phe Thr Arg Gly Asp Gly 100 105 110

Thr Gly Gly Lys Ser Ile Tyr Gly Glu Arg Phe Pro Asp Glu Asn Phe 115 120 125

Lys Leu Lys His Tyr Gly Pro Gly Trp Val Ser Met Ala Asn Ala Gly 130 135 140

Lys Asp Thr Asn Gly Ser Gln Phe Phe Ile Thr Thr Val Lys Thr Ala 145 150 155 160

Trp Leu Asp Gly Lys His Val Val Phe Gly Lys Val Leu Glu Gly Met 165 170 175

Glu Val Val Arg Lys Val Glu Ser Thr Lys Thr Asp Ser Arg Asp Lys 180 185 190

Pro Leu Lys Asp Val Ile Ile Ala Asp Cys Gly Lys Ile Glu Val Glu 195 200 205

Lys Pro Phe Ala Ile Ala Lys Glu 210 215

<210> 132

211> 208

<212> PRT

<213> Homo sapiens

<400> 132

Met Lys Leu Leu Pro Ser Val Val Leu Lys Leu Phe Leu Ala Ala Val 1 10 15

Leu Ser Ala Leu Val Thr Gly Glu Ser Leu Glu Arg Leu Arg Gly 20 25. 30

Leu Ala Ala Gly Thr Ser Asn Pro Asp Pro Pro Thr Val Ser Thr Asp  $35 \ \ \, 40 \ \ \, 45$ 

Gln Leu Leu Pro Leu Gly Gly Gly Arg Asp Arg Lys Val Arg Asp Leu 50 55 60

Gln Glu Ala Asp Leu Asp Leu Leu Arg Val Thr Leu Ser Ser Lys Pro 65 70 75 80

Gln Ala Leu Ala Thr Pro Asn Lys Glu Glu His Gly Lys Arg Lys Lys 85 90 95

Lys Gly Lys Gly Leu Gly Lys Lys Arg Asp Pro Cys Leu Arg Lys Tyr 100 105 110

Lys Asp Phe Cys Ile His Gly Glu Cys Lys Tyr Val Lys Glu Leu Arg 115 120 125

Ala Pro Ser Cys Ile Cys His Pro Gly Tyr His Gly Glu Arg Cys His 130 135 140

Gly Leu Ser Leu Pro Val Glu Asn Arg Leu Tyr Thr Tyr Asp His Thr 145 150 155 160

Thr Ile Leu Ala Val Val Ala Val Val Leu Ser Ser Val Cys Leu Leu 165 170 175

Val Ile Val Gly Leu Leu Met Phe Arg Tyr His Arg Arg Gly Gly Tyr 180 185 190

Asp Val Glu Asn Glu Glu Lys Val Lys Leu Gly Met Thr Asn Ser His 195 200 205

<210> 13

<211> 178 <212> PRT

<213> Homo sapiens

<400> 133

Met Thr Thr Leu Arg Ala Phe Thr Cys Asp Asp Leu Phe Arg Phe Asn 1  $\phantom{\Big|}$  10  $\phantom{\Big|}$  15

Leu Gln Tyr Leu Ala His Trp Pro Glu Tyr Phe Ile Val Ala Glu Ala . 35 40 40 45

Pro Gly Gly Glu Leu Met Gly Tyr Ile Met Gly Lys Ala Glu Gly Ser 50 60

Val Ala Arg Glu Glu Trp His Gly His Val Thr Ala Leu Ser Val Ala 65 70 75 80

Pro Glu Phe Arg Arg Leu Gly Leu Ala Ala Lys Leu Met Glu Leu Leu 95 90 95

Glu Glu Ile Ser Glu Arg Lys Gly Gly Phe Phe Val Asp Leu Phe Val 100 105 110

Arg Val Ser Asn Gln Val Ala Val Asn Met Tyr Lys Gln Leu Gly Tyr 115 120 125

Ser Val Tyr Arg Thr Val Ile Glu Tyr Tyr Ser Ala Ser Asn Gly Glu 130  $\,$  140

Pro Asp Glu Asp Ala Tyr Asp Met Arg Lys Ala Leu Ser Arg Asp Thr 145 150 150 155 160

Glu Lys Lys Ser Ile Ile Pro Leu Pro His Pro Val Arg Pro Glu Asp 165 170 175

Ile Glu

<210> 134

<211> 185

<213> Homo sapiens

<400> 134

Met Gly Pro Glu Arg His Leu Ser Gly Ala Pro Ala Arg Met Ala Thr 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Val Val Leu Gly Gly Asp Thr Met Gly Pro Glu Arg Ile Phe Pro Asn  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Gln Thr Glu Glu Leu Gly His Gln Gly Pro Ser Glu Gly Thr Gly Asp  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Trp Ser Ser Glu Glu Pro Glu Glu Glu Gin Giu Giu Thr Giy Ser Giy 50 . 55 60

Pro Ala Gly Tyr Ser Tyr Gln Pro Leu Asn Gln Asp Pro Glu Gln Glu 65 70 75 80

Glu Val Glu Leu Ala Pro Val Gly Asp Gly Asp Val Val Ala Asp Ile 85 90 95

Gln Asp Arg Ile Gln Ala Leu Gly Leu His Leu Pro Asp Pro Pro Leu 100 105 110

Glu Ser Glu Asp Glu Asp Glu Glu Glu Gly Ala Thr Ala Leu Asn Asn His 115 120 125

Met Ala Gly Val Ser Leu Pro Ala Pro Gly Val Pro Ala Trp Ala Arg 145 150 150 155 160

Glu Ile Ser Asp Ala Gln Trp Glu Asp Val Val Gln Lys Ala Leu Gln 165 170 175

Ala Arg Gln Ala Ser Pro Ala Trp Lys 180 185

<210> 135 <211> 397

PRT Homo sapiens

Met Asn Ala Gly Ser Asp Pro Val Val Ile Val Ser Ala Ala Arg Thr 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Ile Ile Gly Ser Phe Asn Gly Ala Leu Ala Ala Val Pro Val Gln Asp  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$ 

Leu Gly Ser Thr Val Ile Lys Glu Val Leu Lys Arg Ala Thr Val Ala 35  $\phantom{\bigg|}40\phantom{\bigg|}40\phantom{\bigg|}45\phantom{\bigg|}$ 

Pro Glu Asp Val Ser Glu Val Ile Phe Gly His Val Leu Ala Ala Gly 50 55

Cys Gly Gln Asn Pro Val Arg Gln Ala Ser Val Gly Ala Gly IIe Pro 65 70 75 80

Tyr Ser Val Pro Ala Trp Ser Cys Gln Met Ile Cys Gly Ser Gly Leu 85 90 95

Lys Ala Val Cys Leu Ala Val Gln Ser Ile Gly Ile Gly Asp Ser Ser 100 105 110

Ile Val Val Ala Gly Gly Met Glu Asn Met Ser Lys Ala Pro His Leu 115  $\phantom{\bigg|}120\phantom{\bigg|}$  125

Ala Tyr Leu Arg Thr Gly Val Lys Ile Gly Glu Met Pro Leu Thr Asp 130 135 140

Ser Ile Leu Cys Asp Gly Leu Thr Asp Ala Phe His Asn Cys His Met 145 150 160

Gly Ile Thr Ala Glu Asn Val Ala Thr Lys Trp Gln Val Ser Arg Glu 165 170 175

Asp Gln Asp Lys Val Ala Val Leu Ser Gln Asn Arg Thr Glu Asn Ala 180 185 190

Gln Lys Ala Gly His Phe Asp Lys Glu Ile Val Pro Val Leu Val Ser 195 200 205

Thr Arg Lys Gly Leu Ile Glu Val Lys Thr Asp Glu Phe Pro Arg His 210 215 220

Gly Ser Asn Ile Glu Ala Met Ser Lys Leu Lys Pro Tyr Phe Leu Thr 225 230 235 240

Asp Gly Thr Gly Thr Val Thr Pro Ala Asn Ala Ser Gly Ile Asn Asp 245 250 255

Gly Ala Ala Ala Val Ala Leu Met Lys Lys Ser Glu Ala Asp Lys Arg 260 265 270

Gly Leu Thr Pro Leu Ala Arg Ile Val Ser Trp Ser Gln Val Gly Val  $275 \hspace{1cm} 280 \hspace{1cm} 285$ 

Glu Pro Ser Ile Met Gly Ile Gly Pro Ile Pro Ala Ile Lys Gln Ala 290 295 300

Val Thr Lys Ala Gly Trp Ser Leu Glu Asp Val Asp Ile Phe Glu Ile 305 310 315 320

Asn Glu Ala Phe Ala Ala Val Ser Ala Ala Ile Val Lys Glu Leu Gly 325  $\phantom{\bigg|}330\phantom{\bigg|}330\phantom{\bigg|}335\phantom{\bigg|}$ 

Leu Asn Pro Glu Lys Val Asn Ile Glu Gly Gly Ala Ile Ala Leu Gly 340 345 350

His Pro Leu Gly Ala Ser Gly Cys Arg Ile Leu Val Thr Leu Leu His  $355 \hspace{1.5cm} 360 \hspace{1.5cm} 365$ 

Thr Leu Glu Arg Met Gly Arg Ser Arg Gly Val Ala Ala Leu Cys Ile 370 380

Gly Gly Gly Met Gly Ile Ala Met Cys Val Gln Arg Glu 385  $\phantom{0}$  390  $\phantom{0}$  395

Z2105 136

<211> 556

<213> Homo sapiens

<400> 136

Met Glu Gly Pro Leu Ser Val Phe Gly Asp Arg Ser Thr Gly Glu Thr 1 5 10 15

Ile Arg Ser Gln Asn Val Met Ala Ala Ala Ser Ile Ala Asn Ile Val 20 25 30 Lys Ser Ser Leu Gly Pro Val Gly Leu Asp Lys Met Leu Val Asp Asp 35 40 45

Ile Gly Asp Val Thr Ile Thr Asn Asp Gly Ala Thr Ile Leu Lys Leu 50 60

Leu Glu Val Glu His Pro Ala Ala Lys Val Leu Cys Glu Leu Ala Asp 65 70 75 80

Leu Gln Asp Lys Glu Val Gly Asp Gly Thr Thr Ser Val Val Ile Ile 85 90 95

Ala Ala Glu Leu Leu Lys Asn Ala Asp Glu Leu Val Lys Gln Lys Ile 100 105 110

His Pro Thr Ser Val Ile Ser Gly Tyr Arg Leu Ala Cys Lys Glu Ala 115 120 125

Val Arg Tyr Ile Asn Glu Asn Leu Ile Val Asn Thr Asp Glu Leu Gly 130 135 140

Arg Asp Cys Leu Ile Asn Ala Ala Lys Thr Ser Met Ser Ser Lys Ile 145 : 150 : 155 : 160

Ile Gly Ile Asn Gly Asp Phe Phe Ala Asn Met Val Val Asp Ala Val 165 170 175

Leu Ala Ile Lys Tyr Thr Asp Ile Arg Gly Gln Pro Arg Tyr Pro Val

Asn Ser Val Asn Ile Leu Lys Ala His Gly Arg Ser Gli Met Glu Ser 195 200 205

Met Leu Ile Ser Gly Tyr Ala Leu Asn Cys Val Val Gly Ser Gln Gly 210 215 220

Met Pro Lys Arg Ile Val Asn Ala Lys Ile Ala Cys Leu Asp Phe Ser 225 230 235 240

Leu Gln Lys Thr Lys Met Lys Leu Gly Val Gln Val Val Ile Thr Asp 245  $\phantom{0}$  250  $\phantom{0}$  255

Pro Glu Lys Leu Asp Gln Ile Arg Gln Arg Glu Ser Asp Ile Thr Lys 260 265 270

Glu Arg Ile Gln Lys Ile Leu Ala Thr Gly Ala Asn Val Ile Leu Thr  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285$ 

Thr Gly Gly Ile Asp Asp Met Cys Leu Lys Tyr Phe Val Glu Ala Gly 290 295 300

Ala Met Ala Val Arg Arg Val Leu Lys Arg Asp Leu Lys Arg Ile Ala 305 310 315 320

Lys Ala Ser Gly Ala Thr Ile Leu Ser Thr Leu Ala Asn Leu Glu Gly 325 330 335

Glu Glu Thr Phe Glu Ala Ala Met Leu Gly Gln Ala Glu Glu Val Val 340 345 350

Gln Glu Arg Ile Cys Asp Asp Glu Leu Ile Leu Ile Lys Asn Thr Lys 355 360 365

Ala Arg Thr Ser Ala Ser Ile Ile Leu Arg Gly Ala Asn Asp Phe Met 370 380

Cys Asp Glu Met Glu Arg Ser Leu His Asp Ala Leu Cys Val Val Lys 385 390 395 400

Arg Val Leu Glu Ser Lys Ser Val Val Pro Gly Gly Gly Ala Val Glu 405 410 415

Ala Ala Leu Ser Ile Tyr Leu Glu Asn Tyr Ala Thr Ser Met Gly Ser 420 425 430

Arg Glu Gln Leu Ala Ile Ala Glu Phe Ala Arg Ser Leu Leu Val Ile 435  $\phantom{\bigg|}440\phantom{\bigg|}$  445

Ala Lys Leu Arg Ala Phe His Asn Glu Ala Gln Val Asn Pro Glu Arg 465 470 480

Lys Asn Leu Lys Trp Ile Gly Leu Asp Leu Ser Asn Gly Lys Pro Arg 485 490 490 495

Asp Asn Lys Gln Ala Gly Val Phe Glu Pro Thr Ile Val Lys Val Lys 500 505 510

Ser Leu Lys Phe Ala Thr Glu Ala Ala Ile Thr Ile Leu Arg Ile Asp 515 520 525

Asp Leu Ile Lys Leu His Pro Glu Ile Leu Arg Ile Lys His Gly Ser 530 540

Tyr Glu Asp Ala Val His Ser Gly Ala Leu Asn Asp 545 555 555

<210> 137

<211> 266

<212> PRT <213> Homo sapiens

<400> 137

Met Pro Lys Gly Lys Lys Ala Lys Gly Lys Lys Val Ala Pro Ala Pro 1 5 10 15

Ala Val Val Lys Lys Gln Glu Ala Lys Lys Val Val Asn Pro Leu Phe 20 25 30

Glu Lys Arg Pro Lys Asn Phe Gly Ile Gly Gln Asp Ile Gln Pro Lys  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Arg Asp Leu Thr Arg Phe Val Lys Trp Pro Arg Tyr Ile Arg Leu Gln 50 60

Arg Gln Arg Ala Ile Leu Tyr Lys Arg Leu Lys Val Pro Pro Ala Ile 65 70 75 80

Asn Gln Phe Thr Gln Ala Leu Asp Arg Gln Thr Ala Thr Gln Leu Leu 85 90 95

Lys Leu Ala His Lys Tyr Arg Pro Glu Thr Lys Gln Glu Lys Lys Gln 100 105 110

Arg Leu Leu Ala Arg Ala Glu Lys Lys Ala Ala Gly Lys Gly Asp Val 115 120 125

Pro Thr Lys Arg Pro Pro Val Leu Arg Ala Gly Val Asn Thr Val Thr 130 135 140

Thr Leu Val Glu Asn Lys Lys Ala Gln Leu Val Val Ile Ala His Asp 145 150 155 160

Val Asp Pro Ile Glu Leu Val Val Phe Leu Pro Ala Leu Cys Arg Lys 165 170 175

Met Gly Val Pro Tyr Cys Ile Ile Lys Gly Lys Ala Arg Leu Gly Arg 180 185 190

Leu Val His Arg Lys Thr Cys Thr Thr Val Ala Phe Thr Gln Val Asn 195  $\phantom{\bigg|}200\phantom{\bigg|}$ 

Ser Glu Asp Lys Gly Ala Leu Ala Lys Leu Val Glu Ala Ile Arg Thr 210 215 220

Asn Tyr Asn Asp Arg Tyr Asp Glu Ile Arg Arg His Trp Gly Gly Asn 225 230 235 240

Val Leu Gly Pro Lys Ser Val Ala Arg Ile Ala Lys Leu Glu Lys Ala 245 250 255

Lys Ala Lys Glu Leu Ala Thr Lys Leu Gly 260 265

<210> 138

<211> 160

<212> PRT

<213> Homo sapiens

<400> 138

Met Asp Cys Gln Asn Gly His Gln His Ile Ser Gln Glu Leu Glu Val 1 5 10 15

Leu Arg Ile His Met Gln Leu Val Thr Val Gln Phe Thr Gln Leu Gly 20 25 30

Lys Gly Ala Leu Glu Ile Ile Gln Val Leu Cys Gly Ile Ser Gln Gly  $35 \hspace{1cm} 40 \hspace{1cm} 45 \hspace{1cm}$ 

Ser Gln His Leu Leu Ala Met Cys Leu Asp Phe Gly Val Ala His Asp 50 60

Gly Arg Gly Arg Gln Val Ala Lys Ala Val Lys Glu Pro Leu Gly 65 70 75 80

Pro Trp Val Asp Asn Gln Glu Pro Ser Gln Gly Phe Ser Ser Ser Ile  $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Phe His Ile His Leu Ala Pro Gln Ala Cys Asp Ser Ser Leu Val Leu 100 105 110

Leu Cys Glu Met Thr His Gly Val Trp Thr Arg Ser Leu Leu Ile Thr 115  $$\rm 120$$ 

Ser Asp Val Pro Glu Ala Ser Val Thr Gln Ile Leu Leu Cys Ala Met 130 135 140

Trp Thr Leu Pro Ser His Ala Thr Thr Arg Glu Leu Thr Gln Trp Val 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}160\phantom{\bigg|}$ 

<210> 139

<211> 172

<212> PRT

<213> Homo sapiens

<400> 139

Met Ile Ile Tyr Arg Asp Leu Ile Ser His Asp Glu Met Phe Ser Asp 1 10 15

Gly Lys Met Val Ser Arg Thr Glu Gly Asn Ile Asp Asp Ser Leu Ile  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Gly Gly Asn Ala Ser Ala Glu Gly Pro Glu Gly Glu Gly Thr Glu Ser 50

Thr Val Ile Thr Gly Val Asp Ile Val Met Asn His His Leu Gln Glu 65 70 75 80

Thr Ser Phe Thr Lys Glu Ala Tyr Lys Lys Tyr Ile Lys Asp Tyr Met  $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Lys Ser Ile Lys Gly Lys Leu Glu Glu Gln Arg Pro Glu Arg Val Lys 100 105 110

Pro Phe Met Thr Gly Ala Ala Glu Gln Ile Lys His Ile Leu Ala Asn 115 120 125

Phe Lys Asn Tyr Gln Phe Phe Ile Gly Glu Asn Met Asn Pro Asp Gly 130 135 140

Met Val Ala Leu Leu Asp Tyr Arg Glu Asp Gly Val Thr Pro Tyr Met 145 150 150 160

Ile Phe Phe Lys Asp Gly Leu Glu Met Glu Lys Cys 165 170

<210> 140

<211> 133 <212> PRT

<213> Homo sapiens

<400> 140

Leu Leu Gln Arg Lys Gln Met Val Ile Asp var Leu His Pro Gry Lys 20 25 30

Ala Thr Val Pro Lys Thr Glu Ile Arg Glu Lys Leu Ala Lys Met Tyr  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Lys Thr Thr Pro Asp Val Ile Phe Val Phe Gly Phe Arg Thr His Phe 50 55 60

Gly Gly Gly Lys Thr Thr Gly Phe Gly Met Ile Tyr Asp Ser Leu Asp 65 70 80

Tyr Ala Lys Lys Asn Glu Pro Lys His Arg Leu Ala Arg His Gly Leu 85 90 95

Tyr Glu Lys Lys Lys Thr Ser Arg Lys Gln Arg Lys Glu Arg Lys Asn 100 105 110

Arg Met Lys Lys Val Arg Gly Thr Ala Lys Ala Asn Val Gly Ala Gly 115 120 125

Lys Lys Pro Lys Glu 130

<210> 141

211> 604

<212> PRT <213> Homo sapiens

<400> 141

Met Asn Ile Val Glu Asn Ser Ile Phe Leu Ser Asn Leu Met Lys Ser 1 10 15

Ala Tyr Thr Phe Glu Leu Lys Tyr Asp Leu Ser Cys Glu Leu Tyr Arg 20 25 30

Met Ser Thr Tyr Ser Thr Phe Pro Ala Gly Val Pro Val Ser Glu Arg 35 40 45

Ser Leu Ala Arg Ala Gly Phe Tyr Tyr Thr Gly Val Asn Asp Lys Val 50  $\,$  60  $\cdot$ 

Lys Cys Phe Cys Cys Gly Leu Met Leu Asp Asn Trp Lys Arg Gly Asp 65 70 75 80

Ser Pro Thr Glu Lys His Lys Lys Leu Tyr Pro Ser Cys Arg Phe Val 85 90 95

Phe Pro Ser Ser Val Thr Asn Ser Thr His Ser Leu Leu Pro Gly Thr 115  $\phantom{\bigg|}125$ 

Glu Asn Ser Gly Tyr Phe Arg Gly Ser Tyr Ser Asn Ser Pro Ser Asn 130 135 140

Pro Val Asn Ser Arg Ala Asn Gln Asp Phe Ser Ala Leu Met Arg Ser 145 150 155 160 Ser Tyr His Cys Ala Met Asn Asn Glu Asn Ala Arg Leu Leu Thr Phe 165 170 175

Gln Thr Trp Pro Leu Thr Phe Leu Ser Pro Thr Asp Leu Ala Lys Ala 180 185 190

Gly Phe Tyr Tyr Ile Gly Pro Gly Asp Arg Val Ala Cys Phe Ala Cys 195 200 205

Gly Gly Lys Leu Ser Asn Trp Glu Pro Lys Asp Asn Ala Met Ser Glu 210 225 220

His'Leu Arg His Phe Pro Lys Cys Pro Phe Ile Glu Asn Gln Leu Gln 225 230 240

Asp Thr Ser Arg Tyr Thr Val Ser Asn Leu Ser Met Gln Thr His Ala 245 250 255

Ala Arg Phe Lys Thr Phe Phe Asn Trp Pro Ser Ser Val Leu Val Asn 260 265 270

Pro Glu Gln Leu Ala Ser Ala Gly Phe Tyr Tyr Val Gly Asn Ser Asp 275 280 285

Asp Val Lys Cys Phe Cys Cys Asp Gly Gly Leu Arg Cys Trp Glu Ser 290 300

Gly Asp Asp Pro Trp Val Gln His Ala Lys Trp Phe Pro Arg Cys Glu 305 310 315 320

Tyr Leu Ile Arg Ile Lys Gly Gln Glu Phe Ile Arg Gln Val Gln Ala 325 330 335

Ser Tyr Pro His Leu Leu Glu Gln Leu Leu Ser Thr Ser Asp Ser Pro 340 345 350

Gly Asp Glu Asn Ala Glu Ser Ser Ile Ile His Phe Glu Pro Gly Glu 355  $\phantom{\bigg|}360\phantom{\bigg|}365\phantom{\bigg|}$ 

Asp His Ser Glu Asp Ala Ile Met Met Asn Thr Pro Val Ile Asn Ala 370  $\phantom{\bigg|}375\phantom{\bigg|}375\phantom{\bigg|}$ 

Ala Val Glu Met Gly Phe Ser Arg Ser Leu Val Lys Gln Thr Val Gln 385 390 395 400

Arg Lys Ile Leu Ala Thr Gly Glu Asn Tyr Arg Leu Val Asn Asp Leu 405 410 415

Val Leu Asp Leu Leu Asn Ala Glu Asp Glu Ile Arg Glu Glu Glu Arg 420 425 430

Glu Arg Ala Thr Glu Glu Lys Glu Ser Asn Asp Leu Leu Leu Ile Arg 435 440 445

Lys Asn Arg Met Ala Leu Phe Gln His Leu Thr Cys Val Ile Pro Ile 450 455 460

Leu Asp Ser Leu Leu Thr Ala Gly Ile Ile Asn Glu Gln Glu His Asp 465 470 475 480

Val Ile Lys Gln Lys Thr Gln Thr Ser Leu Gln Ala Arg Glu Leu Ile 485  $^{\circ}$  490  $^{\circ}$  495

Asp Thr Ile Leu Val Lys Gly Asn Ile Ala Ala Thr Val Phe Arg Asn  $500 \hspace{1.5cm} 505 \hspace{1.5cm} 510$ 

Ser Leu Gln Glu Ala Glu Ala Val Leu Tyr Glu His Leu Phe Val Gln  $515 \hspace{1.5cm} 525 \hspace{1.5cm}$ 

Gln Asp Ile Lys Tyr Ile Pro Thr Glu Asp Val Ser Asp Leu Pro Val 530 535 540

Glu Glu Gln Leu Arg Arg Leu Gln Glu Glu Arg Thr Cys Lys Val Cys 545 550 555 560

Met Asp Lys Glu Val Ser Ile Val Phe Ile Pro Cys Gly His Leu Val 565 570 575

Val Cys Lys Asp Cys Ala Pro Ser Leu Arg Lys Cys Pro Ile Cys Arg 580 585 590

Ser Thr Ile Lys Gly Thr Val Arg Thr Phe Leu Ser 595 600

<210> 142

<211> 624

<212> PRT

<213> Homo sapiens

<400> 142

Met Gln Pro Asp Pro Arg Pro Ser Gly Ala Gly Ala Cys Cys Arg Phe 1 5 10 15

Leu Pro Leu Gln Ser Gln Cys Pro Glu Gly Ala Gly Asp Ala Val Met  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Tyr Ala Ser Thr Glu Cys Lys Ala Glu Val Thr Pro Ser Gln His Gly  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

As Arg Thr Phe Ser Tyr Thr Leu Glu Asp His Thr Lys Gln Ala Phe 50  $\,$  60  $\,$ 

Gly Ile Met Asn Glu Leu Arg Leu Ser Gln Gln Leu Cys Asp Val Thr 65 70 75 80

Leu Gln Val Lys Tyr Gln Asp Ala Pro Ala Ala Gln Phe Met Ala His 90 90 95

Lys Val Val Leu Ala Ser Ser Ser Pro Val Phe Lys Ala Met Phe Thr  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

Asn Gly Leu Arg Glu Gln Gly Met Glu Val Val Ser Ile Glu Gly Ile 115 120 125

His Pro Lys Val Met Glu Arg Leu Ile Glu Phe Ala Tyr Thr Ala Ser 130 135 140

Ile Ser Met Gly Glu Lys Cys Val Leu His Val Met Asn Gly Ala Val 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ 

Met Tyr Gln Ile Asp Ser Val Val Arg Ala Cys Ser Asp Phe Leu Val 165 170 175Gln Gln Leu Asp Pro Ser Asn Ala Ile Gly Ile Ala Asn Phe Ala Glu 180 185 190 Gln Ile Gly Cys Val Glu Leu His Gln Arg Ala Arg Glu Tyr Ile Tyr 195 200 205 Met His Phe Gly Glu Val Ala Lys Gln Glu Glu Phe Phe Asn Leu Ser 210 215 220 His Cys Gln Leu Val Thr Leu Ile Ser Arg Asp Asp Leu Asn Val Arg 225 230 235 240 Cys Glu Ser Glu Val Phe His Ala Cys Ile Asn Trp Val Lys Tyr Asp  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255 \hspace{1.5cm}$ Cys Glu Gln Arg Arg Phe Tyr Val Gln Ala Leu Leu Arg Ala Val Arg 260 265 270Cys His Ser Leu Thr Pro Asn Phe Leu Gln Met Gln Leu Gln Lys Cys 275 280 285Glu Ile Leu Gln Ser Asp Ser Arg Cys Lys Asp Tyr Leu Val Lys Ile 290 295 300 Phe Glu Glu Leu Thr Leu His Lys Pro Thr Gln Val Met Pro Cys Arg 305 310 315 320 Ala Pro Lys Val Gly Arg Leu Ile Tyr Thr Ala Gly Gly Tyr Phe Arg 325 330 335 Gln Ser Leu Ser Tyr Leu Glu Ala Tyr Asn Pro Ser Asn Gly Thr Trp 340 345 350Leu Arg Leu Ala Asp Leu Gln Val Pro Arg Ser Gly Leu Ala Gly Cys 355 360 365Val Val Gly Gly Leu Leu Tyr Ala Val Gly Gly Arg Asn Asn Ser Pro 370 375 380 Asp Gly Asn Thr Asp Ser Ser Ala Leu Asp Cys Tyr Asn Pro Met Thr 385 390 395 400

Gly Val Gly Val Ile Asp Gly His Ile Tyr Ala Val Gly Gly Ser His
420 425 430

Asn Gln Trp Ser Pro Cys Ala Pro Met Ser Val Pro Arg Asn Arg Ile 405 410 415

Gly Cys Ile His His Asn Ser Val Glu Arg Tyr Glu Pro Glu Arg Asp 435 440 445

Glu Trp His Leu Val Ala Pro Met Leu Thr Arg Arg Ile Gly Val Gly 450 455 460

Val Ala Val Leu Asn Arg Leu Leu Tyr Ala Val Gly Gly Phe Asp Gly 465 470 475 480

Thr Asn Arg Leu Asn Ser Ala Glu Cys Tyr Tyr Pro Glu Arg Asn Glu
485 490 495

Trp Arg Met Ile Thr Ala Met Asn Thr Ile Arg Ser Gly Ala Gly Val $500 \hspace{1.5cm} 505 \hspace{1.5cm} 510$ 

Cys Val Leu His Asn Cys Ile Tyr Ala Ala Gly Gly Tyr Asp Gly Gln  $515 \hspace{1.5cm} 520 \hspace{1.5cm} 525$ 

Asp Gln Leu Asn Ser Val Glu Arg Tyr Asp Val Glu Thr Glu Thr Trp 530 540

Thr Phe Val Ala Pro Met Lys His Arg Arg Ser Ala Leu Gly Ile Thr 545 550 555 560

Val His Gln Gly Arg Ile Tyr Val Leu Gly Gly Tyr Asp Gly His Thr 565 570 575

Phe Leu Asp Ser Val Glu Cys Tyr Asp Pro Asp Thr Asp Thr Trp Ser 580 585 590

Glu Val Thr Arg Met Thr Ser Gly Arg Ser Gly Val Gly Val Ala Val 595 600 605

Thr Met Glu Pro Cys Arg Lys Gln Ile Asp Gln Gln Asn Cys Thr Cys 610 620

<210> 143

<211> 389

<212> PRT

<213> Homo sapiens

<400> 143

Met Leu Ser Leu Arg Val Pro Leu Ala Pro Ile Thr Asp Pro Gln Gln 1 10 15

Leu Gln Leu Ser Pro Leu Lys Gly Leu Ser Leu Val Asp Lys Glu Asn  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$ 

Thr Pro Pro Ala Leu Ser Gly Thr Arg Val Leu Ala Ser Lys Thr Ala 35 40 45

Arg Arg Ile Phe Gln Glu Pro Thr Glu Pro Lys Thr Lys Ala Ala Ala 50 55 60

Pro Gly Val Glu Asp Glu Pro Leu Leu Arg Glu Asn Pro Arg Arg Phe 65 70 75 80

Val Ile Phe Pro Ile Glu Tyr His Asp Ile Trp Gln Met Tyr Lys Lys 85 90 95

Ala Glu Ala Ser Phe Trp Thr Ala Glu Glu Val Asp Leu Ser Lys Asp 100 105 110

Ile Gln His Trp Glu Ser Leu Lys Pro Glu Glu Arg Tyr Phe Ile Ser 115 120 125

His Val Leu Ala Phe Phe Ala Ala Ser Asp Gly Ile Val Asn Glu Asn 130 135 140

Leu Val Glu Arg Phe Ser Gln Glu Val Gln Ile Thr Glu Ala Arg Cys 145 150 155 160

Phe Tyr Gly Phe Gln Ile Ala Met Glu Asn Ile His Ser Glu Met Tyr 165 170 175

Ser Leu Leu Ile Asp Thr Tyr Ile Lys Asp Pro Lys Glu Arg Glu Phe 180 185 190

Leu Phe Asn Ala Ile Glu Thr Met Pro Cys Val Lys Lys Lys Ala Asp 195 200 205

Trp Ala Leu Arg Trp Ile Gly Asp Lys Glu Ala Thr Tyr Gly Glu Arg 210 215 220

Val Val Ala Phe Ala Ala Val Glu Gly Ile Phe Phe Ser Gly Ser Phe 225 230 235 240

Ala Ser Ile Phe Trp Leu Lys Lys Arg Gly Leu Met Pro Gly Leu Thr 245 250 255

Phe Ser Asn Glu Leu Ile Ser Arg Asp Glu Gly Leu His Cys Asp Phe 260 265 270

Ala Cys Leu Met Phe Lys His Leu Val His Lys Pro Ser Glu Glu Arg 275 280 285

Val Arg Glu Ile Ile Asn Ala Val Arg Ile Glu Gln Glu Phe Leu 290 295 300

Thr Glu Ala Leu Pro Val Lys Leu Ile Gly Met Asn Cys Thr Leu Met 305 310 315 320

Lys Gln Tyr Ile Glu Phe Val Ala Asp Arg Leu Met Leu Glu Leu Gly 325 335

Phe Ser Lys Val Phe Arg Val Glu Asn Pro Phe Asp Phe Met Glu Asn 340  $\phantom{\bigg|}345\phantom{\bigg|}$ 

Ile Ser Leu Glu Gly Lys Thr Asn Phe Phe Glu Lys Arg Val Gly Glu 355  $\phantom{\bigg|}360\phantom{\bigg|}$ 

Tyr Gln Arg Met Gly Val Met Ser Ser Pro Thr Glu Asn Ser Phe Thr 370 380

Leu Asp Ala Asp Phe

<210> 144

<211> 281

<212> PRT <213> Homo sapiens

<400> 144

Met Ala Thr Asn Phe Leu Ala His Glu Lys Ile Trp Phe Asp Lys Phe 1 5 10 15

Lys Tyr Asp Asp Ala Glu Arg Arg Phe Tyr Glu Gln Met Asn Gly Pro  $20 \\ 25 \\ 30$ 

Val Arg Gly Ala Ser Arg Gln Glu Asn Gly Ala Thr Val Ile Leu Arg 35 40 45

Asp Ile Ala Arg Ala Arg Glu Asn Ile Gln Lys Ser Leu Ala Gly Ser 50 55 60

Ser Gly Pro Gly Ala Ser Ser Gly Thr Ser Gly Asp His Gly Glu Leu 65 70 75 80

Val Val Arg Ile Ala Ser Leu Glu Val Glu Asn Gln Ser Leu Arg Gly 85 90 95

Val Val Gln Glu Leu Gln Gln Ala Ile Ser Lys Leu Glu Ala Arg Leu 100 105 110

Asn Val Leu Glu Lys Ser Ser Pro Gly His Arg Ala Thr Ala Pro Gln 115 120 125

Thr Gln His Val Ser Pro Met Arg Gln Val Glu Pro Pro Ala Lys Lys 130 135 140

Pro Ala Thr Pro Ala Glu Asp Asp Glu Asp Asp Asp Ile Asp Leu Phe 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ 

Gly Ser Asp Asn Glu Glu Glu Asp Lys Glu Ala Ala Gln Leu Arg Glu 165 170 175

Glu Arg Leu Arg Gln Tyr Ala Glu Lys Lys Ala Lys Lys Pro Ala Leu 180 185 190

Val Ala Lys Ser Ser Ile Leu Leu Asp Val Lys Pro Trp Asp Asp Glu 195 200 205

Thr Asp Met Ala Gln Leu Glu Ala Cys Val Arg Ser Ile Gln Leu Asp  $210 \hspace{1.5cm} 215 \hspace{1.5cm} 220 \hspace{1.5cm}$ 

Gly Leu Val Trp Gly Ala Ser Lys Leu Val Pro Val Gly Tyr Gly Ile 225 230 235 240

Arg Lys Leu Gln Ile Gln Cys Val Val Glu Asp Asp Lys Val Gly Thr 245  $\phantom{0}$  255

Asp Leu Leu Glu Glu Glu Ile Thr Lys Phe Glu Glu His Val Gln Ser 260 265 270

Val Asp Ile Ala Ala Phe Asn Lys Ile 275 280

<210> 145

<211> 269

<212> PRT

<213> Homo sapiens

<400> 145

Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp 1. 5 10 15

Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30 \hspace{1.5cm}$ 

Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp Thr Ile Glu 50 60

Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln 65 70 75 80

Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg 100 105 110

Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr 115 \$120\$

Ile Thr Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala 130 135 140

Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile 145 150 155 160

Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn  $165 \hspace{1.5cm} 170 \hspace{1.5cm} 175$ 

Ile Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly 180 185 190

Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu 195  $\phantom{\bigg|}200\phantom{\bigg|}205\phantom{\bigg|}$ 

Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp 210 215 220

Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys 225 230 235 240

Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu 245 250 255

Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Val  $260 \ \ 265$ 

<210> 146

<211> 1231

<212> PRT

<213> Homo sapiens

<400> 146

Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys 1 10 15

Val Ala Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Leu Thr Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala 35 40 45

Ile Tyr Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Val Ile Met 50 60 Val Cys Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys 65 70 75 80 Gln Lys Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe
85 90 95 Thr Cys Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu 115 120 125Cys Asp Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val 130 \$135\$Lys Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}160\phantom{\bigg|}$ Ala Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe 165 170 175Val Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys 180 185 190 Ser Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile 195 200 205 Ser Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys 210 215 220 Ile Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly 225 230 235 240 Tyr Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255 \hspace{1.5cm}$ Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Cys Asp Asn Pro Tyr Ile 260 265 270 Pro Asn Gly Asp Tyr Ser Pro Leu Arg Ile Lys His Arg Thr Gly Asp 275 280 285 Glu Ile Thr Tyr Gln Cys Arg Asn Gly Phe Tyr Pro Ala Thr Arg Gly 290 295 300 As Thr Ala Lys Cys Thr Ser Thr Gly Trp Ile Pro Ala Pro Arg Cys 305  $\phantom{\bigg|}310\phantom{\bigg|}315\phantom{\bigg|}320\phantom{\bigg|}$ Thr Leu Lys Pro Cys Asp Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr 325 330 335His Glu Asn Met Arg Arg Pro Tyr Phe Pro Val Ala Val Gly Lys Tyr 340 345 350Tyr Ser Tyr Tyr Cys Asp Glu His Phe Glu Thr Pro Ser Gly Ser Tyr 355 360 30

Trp Asp His Ile His Cys Thr Gln Asp Gly Trp Ser Pro Ala Val Pro 370 375 380

Cys Leu Arg Lys Cys Tyr Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln 385 390 395 400

Asn His Gly Arg Lys Phe Val Gln Gly Lys Ser Ile Asp Val Ala Cys  $405 \hspace{1.5cm} 410 \hspace{1.5cm} 415 \hspace{1.5cm}$ 

His Pro Gly Tyr Ala Leu Pro Lys Ala Gln Thr Thr Val Thr Cys Met 420 425 430

Glu Asn Gly Trp Ser Pro Thr Pro Arg Cys Ile Arg Val Lys Thr Cys 435 440 445

Ser Lys Ser Ser Ile Asp Ile Glu Asn Gly Phe Ile Ser Glu Ser Gln 450 455 460

Tyr Thr Tyr Ala Leu Lys Glu Lys Ala Lys Tyr Gln Cys Lys Leu Gly 465 470 475 480

Tyr Val Thr Ala Asp Gly Glu Thr Ser Gly Ser Ile Arg Cys Gly Lys  $485 \hspace{1cm} 490 \hspace{1cm} 495 \hspace{1cm}$ 

Asp Gly Trp Ser Ala Gln Pro Thr Cys Ile Lys Ser Cys Asp Ile Pro  $500 \hspace{1.5cm} 505 \hspace{1.5cm} 510 \hspace{1.5cm}$ 

Val Phe Met Asn Ala Arg Thr Lys Asn Asp Phe Thr Trp Phe Lys Leu 515 520 525

Gly Ser Thr Thr Gly Ser Ile Val Cys Gly Tyr Asn Gly Trp Ser Asp 545 550 555 560

Leu Pro Ile Cys Tyr Glu Arg Glu Cys Glu Leu Pro Lys Ile Asp Val565 570 575

His Leu Val Pro Asp Arg Lys Lys Asp Gln Tyr Lys Val Gly Glu Val 580 585 590

Leu Lys Phe Ser Cys Lys Pro Gly Phe Thr Ile Val Gly Pro Asn Ser  $595 \hspace{1.5cm} 600 \hspace{1.5cm} 605$ 

Val Gln Cys Tyr His Phe Gly Leu Ser Pro Asp Leu Pro Ile Cys Lys 610 615 620

Glu Gln Val Gln Ser Cys Gly Pro Pro Pro Glu Leu Leu Asn Gly Asn 625 630 635 640

Val Lys Glu Lys Thr Lys Glu Glu Tyr Gly His Ser Glu Val Val Glu 645 650 655

Tyr Tyr Cys Asn Pro Arg Phe Leu Met Lys Gly Pro Asn Lys Ile Gln 660 665 670

Cys Val Asp Gly Glu Trp Thr Thr Leu rio vai Cys lie vai Giu Giu Giu

Ser Thr Cys Gly Asp Ile Pro Glu Leu Glu His Gly Trp Ala Gln Leu 690 695 700

Ser Ser Pro Pro Tyr Tyr Tyr Gly Asp Ser Val Glu Phe Asn Cys Ser 705 710 715 720

Glu Ser Phe Thr Met Ile Gly His Arg Ser Ile Thr Cys Ile His Gly 725 730 735

Val Trp Thr Gln Leu Pro Gln Cys Val Ala Ile Asp Lys Leu Lys Lys 740 745 750

Cys Lys Ser Ser Asn Leu Ile Ile Leu Glu Glu His Leu Lys Asn Lys 755 760 765

Lys Glu Phe Asp His Asn Ser Asn Ile Arg Tyr Arg Cys Arg Gly Lys 770 780

Glu Gly Trp Ile His Thr Val Cys Ile Asn Gly Arg Trp Asp Pro Glu 785 790 795 800

Val Asn Cys Ser Met Ala Gln Ile Gln Leu Cys Pro Pro Pro Gln 805 810 815

Ile Pro Asn Ser His Asn Met Thr Thr Thr Leu Asn Tyr Arg Asp Gly 820 825 830

Glu Lys Val Ser Val Leu Cys Gln Glu Asn Tyr Leu Ile Gln Glu Gly 835 840 845

Glu Glu Ile Thr Cys Lys Asp Gly Arg Trp Gln Ser Ile Pro Leu Cys 850 855 860

Val Glu Lys Ile Pro Cys Ser Gln Pro Pro Gln Ile Glu His Gly Thr 865 870 875 880

Ile Asn Ser Ser Arg Ser Ser Gln Glu Ser Tyr Ala His Gly Thr Lys 885 890 895

Leu Ser Tyr Thr Cys Glu Gly Gly Phe Arg Ile Ser Glu Glu Asn Glu 900 905 910

Thr Thr Cys Tyr Met Gly Lys Trp Ser Ser Pro Pro Gln Cys Glu Gly 915 920 925

Leu Pro Cys Lys Ser Pro Pro Glu Ile Ser His Gly Val Val Ala His 930 935 940

Met Ser Asp Ser Tyr Gln Tyr Gly Glu Glu Val Thr Tyr Lys Cys Phe 945 950 950 960

Glu Gly Phe Gly Ile Asp Gly Pro Ala Ile Ala Lys Cys Leu Gly Glu 965 970 975

Lys Trp Ser His Pro Pro Ser Cys Ile Lys Thr Asp Cys Leu Ser Leu 980 985 990

Pro Ser Phe Glu Asn Ala Ile Pro Met Gly Glu Lys Lys Asp Val Tyr 995 1000 1005

- Lys Ala Gly Glu Gln Val Thr Tyr Thr Cys Ala Thr Tyr Tyr Lys 1010 1015 1020
- Met Asp Gly Ala Ser Asn Val Thr Cys Ile Asn Ser Arg Trp Thr  $1025 \\ 1030 \\ 1035$
- Gly Arg Pro Thr Cys Arg Asp Thr Ser Cys Val Asn Pro Pro Thr 1040 1045 1050
- Val Gln Asn Ala Tyr Ile Val Ser Arg Gln Met Ser Lys Tyr Pro 1055 1060 1065
- Ser Gly Glu Arg Val Arg Tyr Gln Cys Arg Ser Pro Tyr Glu Met 1070 1080
- Phe Gly Asp Glu Glu Val Met Cys Leu Asn Gly Asn Trp Thr Glu 1085 1090 1095
- Pro Pro Gln Cys Lys Asp Ser Thr Gly Lys Cys Gly Pro Pro 1100 1110 1110
- Pro Ile Asp Asn Gly Asp Ile Thr Ser Phe Pro Leu Ser Val Tyr 1115 1120 1125
- Ala Pro Ala Ser Ser Val Glu Tyr Gln Cys Gln Asn Leu Tyr Gln 1130 1140
- Leu Glu Gly Asn Lys Arg Ile Thr Cys Arg Asn Gly Gln Trp Ser 1145 1150 1155
- Glu Pro Pro Lys Cys Leu His Pro Cys Val Ile Ser Arg Glu Ile 1160 1165 1170
- Met Glu Asn Tyr Asn Ile Ala Leu Arg Trp Thr Ala Lys Gln Lys 1175 1180 1185
- Leu Tyr Ser Arg Thr Gly Glu Ser Val Glu Phe Val Cys Lys Arg 1190 1195 1200
- Gly Tyr Arg Leu Ser Ser Arg Ser His Thr Leu Arg Thr Thr Cys 1205 1210 1215
- Trp Asp Gly Lys Leu Glu Tyr Pro Thr Cys Ala Lys Arg 1220 1225 1230

- <210> 147 <211> 364 <212> PRT <213> Homo sapiens
- <400> 147
- Met Tyr Leu Ser Arg Phe Leu Ser Ile His Ala Leu Trp Val Thr Val 1 5 10 15
- Ser Ser Val Met Gln Pro Tyr Pro Leu Val Trp Gly His Tyr Asp Leu  $20 \hspace{1cm} 25 \hspace{1cm} 30$

Leu Asp Pro Pro Asp Ile Thr Cys Gly Asp Pro Pro Glu Thr Phe Cys 65 70 75 80

Ala Met Gly Asn Pro Tyr Met Cys Asn Asn Glu Cys Asp Ala Ser Thr  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Pro Glu Leu Ala His Pro Pro Glu Leu Met Phe Asp Phe Glu Gly Arg 100 105 110

His Pro Ser Thr Phe Trp Gln Ser Ala Thr Trp Lys Glu Tyr Pro Lys 115 120 125

Pro Leu Gln Val Asn Ile Thr Leu Ser Trp Ser Lys Thr Ile Glu Leu 130 135 140

Thr Asp Asn Ile Val Ile Thr Phe Glu Ser Gly Arg Pro Asp Gln Met 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ 

Ile Leu Glu Lys Ser Leu Asp Tyr Gly Arg Thr Trp Gln Pro Tyr Gln 165 170 175

Tyr Tyr Ala Thr Asp Cys Leu Asp Ala Phe His Met Asp Pro Lys Ser 180 185 190

Val Lys Asp Leu Ser Gln His Thr Val Leu Glu Ile Ile Cys Thr Glu 195 200 205

Glu Tyr Ser Thr Gly Tyr Thr Thr Asn Ser Lys Ile Ile His Phe Glu 210 215 220

Ile Lys Asp Arg Phe Ala Phe Phe Ala Gly Pro Arg Leu Arg Asn Met 225  $\phantom{\bigg|}230\phantom{\bigg|}230\phantom{\bigg|}235\phantom{\bigg|}240\phantom{\bigg|}$ 

Ala Ser Leu Tyr Gly Gln Leu Asp Thr Thr Lys Lys Leu Arg Asp Phe \$250\$

Phe Thr Val Thr Asp Leu Arg Ile Arg Leu Leu Arg Pro Ala Val Gly 260 265 270

Glu Ile Phe Val Asp Glu Leu His Leu Ala Arg Tyr Phe Tyr Ala Ile 275 280 285

Ser Asp Ile Lys Val Arg Gly Arg Cys Lys Cys Asn Leu His Ala Thr 290 295 300

Val Cys Val Tyr Asp Asn Ser Lys Leu Thr Cys Glu Cys Glu His Asn 305 310 315 320

Thr Thr Gly Pro Asp Cys Gly Lys Cys Lys Lys Asn Tyr Gln Gly Arg 325 330 335

Pro Trp Ser Pro Gly Ser Tyr Leu Pro Ile Pro Lys Gly Thr Ala Asn 340 345 350

Thr Cys Ile Pro Ser Ile Ser Ser Ile Gly Ser Lys 355 360

<210> 148

<211> 3210

<212> PRT

<213> Homo sapiens

<400> 148

Met Ser Trp Ala Leu Glu Glu Trp Lys Glu Gly Leu Pro Thr Arg Thr 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Leu Gln Lys Ile Gln Glu Leu Glu Gly Gln Leu Asp Lys Lys Lys 20 25 30

Glu Lys Gln Gln Arg Gln Phe Gln Leu Asp Ser Leu Glu Ala Ala Pro  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Gln Lys Gln Thr Gln Lys Val Glu Asn Glu Lys Thr Glu Gly Thr Asn 50 60

Leu Lys Arg Glu Asn Gln Arg Leu Met Glu Ile Cys Glu Ser Leu Glu 65 70 75 80

Lys Thr Lys Gln Lys Ile Ser His Glu Leu Gln Val Lys Glu Ser Gln 85 90 95

Val Asn Phe Gln Glu Gly Gln Leu Asn Ser Gly Lys Lys Gln Ile Glu 100 105 110

Lys Leu Glu Gln Glu Leu Lys Arg Cys Lys Ser Glu Leu Glu Arg Ser 115 120 125

Gln Gln Ala Ala Gln Ser Ala Asp Val Ser Leu Asn Pro Cys Asn Thr 130 140

Pro Gln Lys Ile Phe Thr Thr Pro Leu Thr Pro Ser Gln Tyr Tyr Ser 145 150 155 160

Gly Ser Lys Tyr Glu Asp Leu Lys Glu Lys Tyr Asn Lys Glu Val Glu 165 170 175

Glu Arg Lys Arg Leu Glu Ala Glu Val Lys Ala Leu Gln Ala Lys Lys 180 185 190

Ala Ser Gln Thr Leu Pro Gln Ala Thr Met Asn His Arg Asp Ile Ala 195 200 205

Arg His Gln Ala Ser Ser Ser Val Phe Ser Trp Gln Gln Glu Lys Thr 210 225 220

Pro Ser His Leu Ser Ser Asn Ser Gln Arg Thr Pro Ile Arg Arg Asp 225 230 235 240

Phe Ser Ala Ser Tyr Phe Ser Gly Glu Leu Glu Val Thr Pro Ser Arg 245 250 255

Ser Thr Leu Gln Ile Gly Lys Arg Asp Ala Asn Ser Ser Phe Phe Gly 260 265 270

Asn Ser Ser Fro His Leu Leu Asp Gln Leu Lys Ala Gln Asn Gln 275 280 285 Glu Leu Arg Asn Lys Ile Asn Glu Leu Glu Leu Arg Leu Gln Gly His 290 295 300Glu Lys Glu Met Lys Gly Gln Val Asn Lys Phe Gln Glu Leu Gln Leu 305 310 315 320 Gln Leu Glu Lys Ala Lys Val Glu Leu Ile Glu Lys Glu Lys Val Leu 325  $\phantom{\bigg|}$  330  $\phantom{\bigg|}$  335 Asn Lys Cys Arg Asp Glu Leu Val Arg Thr Thr Ala Gln Tyr Asp Gln 340 345 350 Ala Ser Thr Lys Tyr Thr Ala Leu Glu Gln Lys Leu Lys Leu Thr 355  $\phantom{000}360\phantom{000}$  365 Glu Asp Leu Ser Cys Gln Arg Gln Asn Ala Glu Ser Ala Arg Cys Ser 370 375 380Leu Glu Gln Lys Ile Lys Glu Lys Glu Lys Glu Phe Gln Glu Glu Leu 385 390 395 400 Ser Arg Gln Gln Arg Ser Phe Gln Thr Leu Asp Gln Glu Cys Ile Gln 405 410 415Met Lys Ala Arg Leu Thr Gln Glu Leu Gln Gln Ala Lys Asn Met His 420 425 430Asn Val Leu Gln Ala Glu Leu Asp Lys Leu Thr Ser Val Lys Gln Gln 435 440 445Leu Glu Asn Asn Leu Glu Glu Phe Lys Gln Lys Leu Cys Arg Ala Glu 450 455 460 Gln Ala Phe Gln Ala Ser Gln Ile Lys Glu Asn Glu Leu Arg Arg Ser 465 470 475 480 Met Glu Glu Met Lys Lys Glu Asn Asn Leu Leu Lys Ser His Ser Glu 485 490 495Gln Lys Ala Arg Glu Val Cys His Leu Glu Ala Glu Leu Lys Asn Ile 500 505 510Lys Gln Cys Leu Asn Gln Ser Gln Asn Phe Ala Glu Glu Met Lys Ala 515 520 525 Lys Asn Thr Ser Gln Glu Thr Met Leu Arg Asp Leu Gln Glu Lys Ile  $530 \hspace{1.5cm} 535 \hspace{1.5cm} 540$ Asn Gln Glu Asn Ser Leu Thr Leu Glu Lys Leu Lys Leu Ala Val 545 550 555 560 Ala Asp Leu Glu Lys Gln Arg Asp Cys Ser Gln Asp Leu Leu Lys Lys 565 570 575 Arg Glu His His Ile Glu Gln Leu Asn Asp Lys Leu Ser Lys Thr Glu Page 217

580 585 590

Lys Glu Ser Lys Ala Leu Leu Ser Ala Leu Glu Leu Lys Lys Glu 595  $\,$  600  $\,$  605

Tyr Glu Glu Leu Lys Glu Glu Lys Thr Leu Phe Ser Cys Trp Lys Ser 610 615 620

Glu Asn Glu Lys Leu Leu Thr Gln Met Glu Ser Glu Lys Glu Asn Leu 625  $\phantom{\bigg|}$  630  $\phantom{\bigg|}$  635  $\phantom{\bigg|}$  640

Gln Ser Lys Ile Asn His Leu Glu Thr Cys Leu Lys Thr Gln Gln Ile  $645 \hspace{1.5cm} 650 \hspace{1.5cm} 655$ 

Lys Ser His Glu Tyr Asn Glu Arg Val Arg Thr Leu Glu Met Asp Arg  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670$ 

Glu Asn Leu Ser Val Glu Ile Arg Asn Leu His Asn Val Leu Asp Ser 675 680 685

Lys Ser Val Glu Val Glu Thr Gln Lys Leu Ala Tyr Met Glu Leu Gln 690 700

Gln Lys Ala Glu Phe Ser Asp Gln Lys His Gln Lys Glu Ile Glu Asn 705 710 715 720

Met Cys Leu Lys Thr Ser Gln Leu Thr Gly Gln Val Glu Asp Leu Glu 725  $\phantom{\bigg|}$  730  $\phantom{\bigg|}$  735

His Lys Leu Gln Leu Leu Ser Asn Glu Ile Met Asp Lys Asp Arg Cys 740 745 750

Tyr Gln Asp Leu His Ala Glu Tyr Glu Ser Leu Arg Asp Leu Leu Lys 755 760 765

Ser Lys Asp Ala Ser Leu Val Thr Asn Glu Asp His Gln Arg Ser Leu  $770 \hspace{1.5cm} 780$ 

Leu Ala Phe Asp Gln Gln Pro Ala Met His His Ser Phe Ala Asn Ile 785 790 795 800

Ile Gly Glu Gln Gly Ser Met Pro Ser Glu Arg Ser Glu Cys Arg Leu 805 810 815

Glu Ala Asp Gln Ser Pro Lys Asn Ser Ala Ile Leu Gln Asn Arg Val 820 825 830

Asp Ser Leu Glu Phe Ser Leu Glu Ser Gln Lys Gln Met Asn Ser Asp 835 840 845

Leu Gln Lys Gln Cys Glu Glu Leu Val Gln Ile Lys Gly Glu Ile Glu 850 855 860

Glu Asn Leu Met Lys Ala Glu Gln Met His Gln Ser Phe Val Ala Glu 865 870 875 880

Thr Ser Gln Arg Ile Ser Lys Leu Gln Glu Asp Thr Ser Ala His Gln 895  $\phantom{\bigg|}$ 

Asn Val Val Ala Glu Thr Leu Ser Ala Leu Glu Asn Lys Glu Lys Glu 900 905 910

Leu Gln Leu Leu Asn Asp Lys Val Glu Thr Glu Gln Ala Glu Ile Gln 915 920 925

Glu Leu Lys Lys Ser Asn His Leu Leu Glu Asp Ser Leu Lys Glu Leu 930 935 940

Gln Leu Leu Ser Glu Thr Leu Ser Leu Glu Lys Lys Glu Met Ser Ser 945 950 950 960

Ile Ile Ser Leu Asn Lys Arg Glu Ile Glu Glu Leu Thr Gln Glu Asn 965 970 975

Gly Thr Leu Lys Glu Ile Asn Ala Ser Leu Asn Gln Glu Lys Met Asn 980 985 990

Leu Ile Gln Lys Ser Glu Ser Phe Ala Asn Tyr Ile Asp Glu Arg Glu 995 1000 1005

Lys Ser Ile Ser Glu Leu Ser Asp Gln Tyr Lys Gln Glu Lys Leu 1010 1015 1020

Ile Leu Leu Gln Arg Cys Glu Glu Thr Gly Asn Ala Tyr Glu Asp 1025 1030

Leu Ser Gln Lys Tyr Lys Ala Ala Gln Glu Lys Asn Ser Lys Leu 1040 1050

Glu Cys Leu Leu Asn Glu Cys Thr Ser Leu Cys Glu Asn Arg Lys  $1055 \hspace{1.5cm} 1060 \hspace{1.5cm} 1065$ 

Asn Glu Leu Glu Gln Leu Lys Glu Ala Phe Ala Lys Glu His Gln 1070 \$1075\$

Leu Met Leu Glu Leu Glu Thr Val Gln Gln Ala Leu Arg Ser Glu 1100 1105 1110

Met Thr Asp Asn Gln Asn Asn Ser Lys Ser Glu Ala Gly Gly Leu 1115 1120 1125

Lys Gln Glu Ile Met Thr Leu Lys Glu Glu Gln Asn Lys Met Gln 1130 1140

Lys Glu Val Asn Asp Leu Leu Gln Glu Asn Glu Gln Leu Met Lys 1145 1150 1155

Val Met Lys Thr Lys His Glu Cys Gln Asn Leu Glu Ser Glu Pro 1160  $$1165\$ 

Ile Arg Asn Ser Val Lys Glu Arg Glu Ser Glu Arg Asn Gln Cys 1175 1180 1185

Asn Phe Lys Pro Gln Met Asp Leu Glu Val Lys Glu Ile Ser Leu 1190 1195 1200

	1205	Tyr	Asn	Ala	Gln	Leu 1210		Gln	Leu	Glu	Ala 1215	Met	Leu	Arg
Asn	Lys 1220		Leu	Lys	Leu	Gln 1225	Glu	Ser	Glu	Lys	Glu 1230	Lys	Glu	Cys
Leu	Gln 1235	His	Glu	Leu	Gln	Thr 1240	Ile	Arg	Gly		Leu 1245	Glu	Thr	Ser
Asn	Leu 1250		Asp	Met	Gln	Ser 1255	Gln	Glu	Ile	Ser	Gly 1260	Leu	Lys	Asp
Суз	Glu 1265	Ile	Asp	Ala	Glu	Glu 1270		Tyr	Ile		Gly 1275	Pro	His	Glu
Leu	Ser 1280	Thr	Ser	Gln	Asn	Asp 1285		Ala	His	Leu	Gln 1290		Ser	Leu
Gln	Thr 1295	Thr	Met	Asn	Lys	Leu 1300		Glu	Leu	Glu	Lys 1305	Ile	Cys	Glu
Ile	Leu 1310	Gln	Ala	Glu	Lys	Tyr 1315	Glu	Leu	Val	Thr	Glu 1320	Leu	Asn	Asp
Ser	Arg 1325		Glu	Суз	Ile	Thr 1330	Ala	Thr	Arg	Lys	Met 1335	Ala	Glu	Glu
Val	Gly 1340		Leu	Leu	Asn	Glu 1345		Lys	Ile	Leu	Asn 1350	Asp	Asp	Ser
Gly	Leu 1355		His	Gly	Glu	Leu 1360		Glu	Asp	Ile	Pro 1365		Gly	Glu
Phe	Gly 1370		Gln	Pro	Asn	Glu 1375	Gln	His	Pro	Val	Ser 1380	Leu	Ala	Pro
Leu	Asp 1385	Glu	Ser	Asn	Ser	Туг 1390	Glu	His	Leu	Thr	Leu 1395	Ser	Asp	Lys
Glu	Val 1400	Gln	Met	His	Phe	Ala 1405	Glu	Leu	Gln	Glu	Lys 1410	Phe	Leu	Ser
Leu	Gln 1415	Ser	Glu	His	Lys	Ile 1420	Leu	His	Asp	Gln	His 1425	Cys	Gln	Met
Ser	Ser 1430	Lys	Met	Ser	Glu	Leu 1435	Gln	Thr	Tyr	Val	Asp 1440	Ser	Leu	Lys
Ala	Glu 1445	Asn	Leu	Val	Leu	Ser 1450		Asn	Leu	Arg	Asn 1455	Phe	Gln	Gly
Asp	Leu 1460	Val	Lys	Glu	Met	Gln 1465	Leu	Gly	Leu	Glu	Glu 1470	Gly	Leu	Val
Pro	Ser 1475	Leu	Ser	Ser	Ser	Cys 1480	Val	Pro	Asp	Ser	Ser 1485	Ser	Leu	Ser
Ser	Leu 1490	Gly	Asp	Ser	Ser	Phe 1495		Arg	Ala	Leu	Leu 1500	Glu	Gln	Thr

Gly Asp Met Ser Leu Leu Ser Asn Leu Glu Gly Ala Val Ser Ala 1505 1510 1515 Tyr Val Asp Ser Leu Lys Ala Glu Asn Leu Val Leu Ser Thr Asn 1535  $\phantom{\bigg|}$  1545  $\phantom{\bigg|}$ Leu Arg Asn Phe Gln Gly Asp Leu Val Lys Glu Met Gln Leu Gly 1550 1560 Leu Glu Glu Gly Leu Val Pro Ser Leu Ser Ser Ser Cys Val Pro 1565 1570 1575Asp Ser Ser Ser Leu Ser Ser Leu Gly Asp Ser Ser Phe Tyr Arg 1580 1585 1590 Ala Leu Leu Glu Gln Thr Gly Asp Met Ser Leu Leu Ser Asn Leu 1595 1600 1605 Glu Gly Val Val Ser Ala Asn Gln Cys Ser Val Asp Glu Val Phe 1610 1615 1620Cys Ser Ser Leu Gln Glu Glu Asn Leu Thr Arg Lys Glu Thr Pro  $1625 \hspace{1.5cm} 1630 \hspace{1.5cm} 1635$ Ser Ala Pro Ala Lys Gly Val Glu Glu Leu Glu Ser Leu Cys Glu 1640 1650 Val Tyr Arg Gln Ser Leu Glu Lys Leu Glu Glu Lys Met Glu Ser 1655 1660 1665 Gln Gly Ile Met Lys Asn Lys Glu Ile Gln Glu Leu Glu Gln Leu 1670 1675 1680 Leu Ser Ser Glu Arg Gln Glu Leu Asp Cys Leu Arg Lys Gln Tyr 1685 1690 1695 Leu Ser Glu Asn Glu Gln Trp Gln Gln Lys Leu Thr Ser Val Thr 1700 1705 1710 Leu Glu Met Glu Ser Lys Leu Ala Ala Glu Lys Lys Gln Thr Glu 1715 1720 1725 Gln Leu Ser Leu Glu Leu Glu Val Ala Arg Leu Gln Leu Gln Gly 1730 1740 Leu Asp Leu Ser Ser Arg Ser Leu Leu Gly Ile Asp Thr Glu Asp 1745 1755Ala Ile Gln Gly Arg Asn Glu Ser Cys Asp Ile Ser Lys Glu His 1760 1765 1770 Thr Ser Glu Thr Thr Glu Arg Thr Pro Lys His Asp Val His Gln  $1775 \,$   $1780 \,$   $1785 \,$ Ile Cys Asp Lys Asp Ala Gln Gln Asp Leu Asn Leu Asp Ile Glu Page 221

1800

Lys	Ile 1805	Glu	Thr	Gly	Ala 1810		Lys	Pro	Thr	Gly 1815	Glu	Cys	Ser
Gly	Glu 1820	Ser	Pro	Asp	Thr 1825	Asn	Tyr	Glu	Pro	Pro 1830	Gly	Glu	Asp
Lys	Thr 1835	Gly	Ser	Ser	Glu 1840		Ile	Ser	Glu	Leu 1845	Ser	Phe	Ser
Gly	Pro 1850	Ala	Leu	Val	Pro 1855	Met	Asp	Phe	Leu	Gly 1860	Asn	Gln	Ģlu
Asp	Ile 1865	Asn	Leu	Gln	Leu 1870		Val	Lуs	Glu	Thr 1875	Ser	Asn	Glu
Asn	Leu 1880	Leu	Leu	His	Val 1885	Ile	Glu	Asp	Arg	Asp 1890	Arg	Lys	Val
Glu	Ser 1895	Leu	Asn	Glu	Met 1900		Glu	Leu	Asp	Ser 1905	Lys	Leu	His

1795

1790

Leu Gln Glu Val Gln Leu Met Thr Lys Ile Glu Ala Cys Ile Glu 1910 1915 1920

Leu Glu Lys Ile Val Gly Glu Leu Lys Lys Glu Asn Ser Asp Leu 1925 1930

Ser Glu Lys Leu Glu Tyr Phe Ser Cys Asp His Gln Glu Leu Leu 1940 1945 1950

Gln Arg Val Glu Thr Ser Glu Gly Leu Asn Ser Asp Leu Glu Met 1955 1960 1965

His Ala Asp Lys Ser Ser Arg Glu Asp Ile Gly Asp Asn Val Ala 1970 1975 1980

Lys Val Asn Asp Ser Trp Lys Glu Arg Phe Leu Asp Val Glu Asn 1985 1990 1995

Glu Leu Ser Arg Ile Arg Ser Glu Lys Ala Ser Ile Glu His Glu 2000 2010

Ala Leu Tyr Leu Glu Ala Asp Leu Glu Val Val Gln Thr Glu Lys 2015 2020 2025

Leu Cys Leu Glu Lys Asp Asn Glu Asn Lys Gln Lys Val Ile Val 2030 2035 2040

Cys Leu Glu Glu Glu Leu Ser Val Val Thr Ser Glu Arg Asn Gln 2045 2055

Leu Arg Gly Glu Leu Asp Thr Met Ser Lys Lys Thr Thr Ala Leu 2060 2065 2065

Asp Gln Leu Ser Glu Lys Met Lys Glu Lys Thr Gln Glu Leu Glu 2075 2080 2085

Ser His Gln Ser Glu Cys Leu His Cys Ile Gln Val Ala Glu Ala 2090 2095 2100

- Glu Val Lys Glu Lys Thr Glu Leu Leu Gln Thr Leu Ser Ser Asp  $2105 \hspace{1.5cm} 2110 \hspace{1.5cm} 2115$
- Val Ser Glu Leu Leu Lys Asp Lys Thr His Leu Gln Glu Lys Leu 2120 2125 2130
- Gln Ser Leu Glu Lys Asp Ser Gln Ala Leu Ser Leu Thr Lys Cys 2135 2140 2145
- Glu Leu Glu Asn Gln Ile Ala Gln Leu Asn Lys Glu Lys Glu Leu 2150 . 2160
- Leu Val Lys Glu Ser Glu Ser Leu Gln Ala Arg Leu Ser Glu Ser 2165 2170 2175
- Asp Tyr Glu Lys Leu Asn Val Ser Lys Ala Leu Glu Ala Ala Leu 2180 2185 2190
- Val Glu Lys Gly Glu Phe Ala Leu Arg Leu Ser Ser Thr Gln Glu 2195 2200 2205
- Glu Val His Gln Leu Arg Arg Gly Ile Glu Lys Leu Arg Val Arg 2210 2215 2220
- Ile Glu Ala Asp Glu Lys Lys Gln Leu His Ile Ala Glu Lys Leu 2225 2230 2235
- Lys Glu Arg Glu Arg Glu Asn Asp Ser Leu Lys Asp Lys Val Glu 2240 2245
- Asn Leu Glu Arg Glu Leu Gln Met Ser Glu Glu Asn Gln Glu Leu 2255 2260 2265
- Val Ile Leu Asp Ala Glu Asn Ser Lys Ala Glu Val Glu Thr Leu 2270 2280

- Gln Ile Gln Glu Lys Gln Gly Gln Leu Ser Glu Leu Asp Lys Leu 2315 2320 2325
- Leu Ser Ser Phe Lys Ser Leu Leu Glu Glu Lys Glu Gln Ala Glu 2330 2340
- Ile Gln Ile Lys Glu Glu Ser Lys Thr Ala Val Glu Met Leu Gln 2345 2350 2355
- Asn Gln Leu Lys Glu Leu Asn Glu Ala Val Ala Ala Leu Cys Gly 2360 2365 2370
- Asp Gln Glu Ile Met Lys Ala Thr Glu Gln Ser Leu Asp Pro Pro 2375 2380 2385

								. ~						
Ile	Glu 2390	Glu	Glu	His	Gln	Leu 2395	Arg	Asn	Ser	Ile	Glu 2400	Lys	Leu	Arg
Ala	Arg 2405	Leu	Glu	Ala	Asp	Glu 2410	Lys	Lys	Gln	Leu	Cys 2415	Val	Leu	Gln
Gln	Leu 2420	Lys	Glu	Ser		His 2425	His	Ala	Asp	Leu	Leu 2430	Lys	Gly	Arg
Val	Glu 2435	Asn	Leu	Glu		Glu 2440	Leu	Glu	Ile	Ala	Arg 2445	Thr	Asn	Gln
Glu	His 2450	Ala	Ala	Leu	Glu	Ala 2455	Glu	Asn	Ser	Lys	Gly 2460	Glu	Val	Glu
	Leu 2465	Lys	Ala	Lys		Glu 2470	Gly	Met	Thr	Gln	Ser 2475	Leu	Arg	Gly
Leu	Glu 2480	Leu	Asp	Val	Val	Thr 2485	Ile	Arg	Ser	Glu	Lys 2490	Glu	Asp	Leu
Thr	Asn 2495		Leu	Gln		Glu 2500		Glu	Arg	Ile	Ser 2505	Glu	Leu	Glu
Ile	Ile 2510	Asn	Ser	Ser	Phe	Glu 2515	Asn	Ile	Leu	Gln	Glu 2520	Lys	Glu	Gln
Glu	Lys 2525		Gln	Met	Lys	Glu 2530	Lys	Ser	Ser	Thr	Ala 2535	Met	Glu	Met
Leu	Gln 2540		Gln	Leu	Lys	Glu 2545		Asn	Glu	Arg	Val 2550	Ala	Ala	Leu
His	Asn 2555		Gln	Glu	Ala	Cys 2560		Ala	Lys	Glu	Gln 2565	Asn	Leu	Ser
Ser	Gln 2570		Glu	Cys	Leu	Glu 2575		Glu	Lys	Ala	Gln 2580	Leu	Leu	Gln
Gly	Leu 2585		Glu	Ala	Lys	Asn 2590	Asn	Tyr	Ile	Val	Leu 2595	Gln	Ser	Ser
Val	Asn 2600		Leu	Ile	Gln *	Glu 2605	Val	Glu	Asp	Gly	Lys 2610	Gln	Lys	Leu
Glu	Lys 2615		Asp	Glu	Glu	Ile 2620		Arg	Leu	Lys	Asn 2625	Gln	Ile	Gln
Asp	Gln 2630		Gln	Leu	Val	Ser 2635		Leu	Ser	Gln	Val 2640	Glu	Gly	Glu
His	Gln 2645		Trp	Lys	Glu	Gln 2650		Leu	Glu	Leu	Arg 2655	Asn	Leu	Thr
Val	Glu 2660		Glu	Gln	Lys	Ile 2665		Val	Leu	Gln	Ser 2670		Asn	Ala
Ser	Leu 2675		Asp	Thr	Leu	Glu 2680		Leu	Gln		Ser 2685		Lys	Asn
										ra	ge 22	. 4		

Leu	Glu 2690		Glu	Leu	Glu	Leu 2695		Lys	Met		Lys 2700		Ser	Phe
Val	Glu 2705	Lys	Val	Asn		Met 2710		Ala	Lys	Glu	Thr 2715	Glu	Leu	Gln
Arg	Glu 2720	Met	His	Glu	Met	Ala 2725	Gln	Lys	Thr	Ala	Glu 2730	Leu	Gln	Glu
Glu	Leu 2735	Ser	Gly	Glu		Asn 2740	Arg	Leu	Ala	Gly	Glu 2745	Leu	Gln	Leu
Leu	Leu 2750		Glu	lle		Ser 2755		Lys	Asp	Gln	Leu 2760	Lys	Glu	Leu
Thr	Leu 2765		Asn	Ser	Glu	Leu 2770		Lys	Ser	Leu	Asp 2775	Cys	Met	His
Lys	Asp 2780		Val	Glu		Glu 2785		Lys	Val	Arg	Glu 2790	Glu	Ile	Ala
Glu	Tyr 2795		Leu	Arg	Leu	His 2800		Ala	Glu	Lys	Lys 2805	His	Gln	Ala
Leu	Leu 2810	Leu	Asp	Thr	Asn	Lys 2815	Gln	Tyr	Glu	Val	Glu 2820	Ile	Gln	Thr
	Arg 2825		Lys	Leu		Ser 2830		Glu	Glu		Leu 2835		Ser	Gln
Lys	Leu 2840		Ile	Asp	Leu	Leu 2845		Ser	Ser	Lys	Glu 2850		Leu	Asn
Asn	Ser 2855	Leu	Lys	Ala	Thr	Thr 2860	Gln		Leu	Glu	Glu 2865	Leu	Lys	Lys
Thr	Lys 2870		Asp	Asn		Lys 2875		Val	Asn	Gln	Leu 2880		Lys	Glu
Asn	Glu 2885	Arg	Ala	Gln	Gly	Lys 2890	Met	Lys	Leu	Leu	Ile 2895	Lys	Ser	Cys
Lys	Gln 2900	Leu	Glu	Glu	Glu	Lys 2905	Glu	Ile	Leu	Gln	Lys 2910	Glu	Leu	Ser
Gln	Leu 2915		Ala	Ala	Gln	Glu 2920		Gln	Lys	Thr	Gly 2925		Val	Met
Asp	Thr 2930		Val	Asp	Glu	Leu 2935		Thr	Glu	Ile	Lys 2940		Leu	Lys
Glu	Thr 2945	Leu	Glu	Glu	Lys	Thr 2950		Glu	Ala	Asp	Glu 2955		Leu	Asp
Lys	Туг 2960		Ser	Leu	Leu	Ile 2965	Ser	His	Glu	Lys	Leu 2970		Lys	Ala
Lys	Glu	Met	Leu	Glu	Thr	Gln	Val	Ala	His		Cys ge 22		Gln	Gln

2980 2975 2985 Ser Lys Gln Asp Ser Arg Gly Ser Pro Leu Leu Gly Pro Val Val 2990 . 2995 Pro Gly Pro Ser Pro Ile Pro Ser Val Thr Glu Lys Arg Leu Ser 3005 3010 3015Ser Gly Gln Asn Lys Ala Ser Gly Lys Arg Gln Arg Ser Ser Gly 3020 3025 3030 Ile Trp Glu Asn Gly Gly Gly Pro Thr Pro Ala Thr Pro Glu Ser 3035 3040 Phe Ser Lys Lys Ser Lys Lys Ala Val Met Ser Gly Ile His Pro 3050 3055 Ala Glu Asp Thr Glu Gly Thr Glu Phe Glu Pro Glu Gly Leu Pro 3065 3070 3075Glu Val Val Lys Lys Gly Phe Ala Asp Ile Pro Thr Gly Lys Thr 3080 \$3085\$Ser Pro  $\,$  Tyr Ile Leu Arg Arg  $\,$  Thr Thr Met Ala Thr  $\,$  Arg Thr Ser  $\,$  3095  $\,$   $\,$  3100  $\,$ Pro Arg Leu Ala Ala Gln Lys Leu Ala Leu Ser Pro Leu Ser Leu 3110  $\phantom{\bigg|}$  3115  $\phantom{\bigg|}$  3120 Gly Lys Glu Asn Leu Ala Glu Ser Ser Lys Pro Thr Ala Gly Gly 3125 3130 3135 Ser Arg Ser Gln Lys Val Lys Val Ala Gln Arg Ser Pro Val Asp 3140 3145 3150Ser Gly Thr Ile Leu Arg Glu Pro Thr Thr Lys Ser Val Pro Val 3155 3160 Pro Thr Thr Lys Ser Val Pro Val Asn Asn Leu Pro Glu Arg Ser Pro Thr Asp Ser Pro Arg Glu Gly 3170 3180 Leu Arg Val Lys Arg Gly Arg Leu Val Pro Ser Pro Lys Ala Gly 3185 3190 3195 Leu Glu Ser Lys Gly Ser Glu Asn Cys Lys Val Gln 3205 <210> 149 <211> 108 <212> PRT <213> Homo sapiens <400> 149 Met Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe 1  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Page 226

35 40 45

Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val 50  $\,$ 

Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp 65 70 75 80

Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala 85 90 95

Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu 100 105

<210> 150

<211> 253

<212> PRT

<213> Homo sapiens

<400> 150

Met Ala Arg Ser Leu Leu Leu Pro Leu Gln Ile Leu Leu Leu Ser Leu 1 5 10 15

Ala Leu Glu Thr Ala Gly Glu Glu Ala Gln Gly Asp Lys Ile Ile Asp 20 25 30

Gly Ala Pro Cys Ala Arg Gly Ser His Pro Trp Gln Val Ala Leu Leu  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Ser Gly Asn Gln Leu His Cys Gly Gly Val Leu Val Asn Glu Arg Trp 50 60

Val Leu Thr Ala Ala His Cys Lys Met Asn Glu Tyr Thr Val His Leu 65 70 75 80

Gly Ser Asp Thr Leu Gly Asp Arg Arg Ala Gln Arg Ile Lys Ala Ser  $85 \\ 90 \\ 95$ 

Lys Ser Phe Arg His Pro Gly Tyr Ser Thr Gln Thr His Val Asn Asp  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105 \hspace{1.5cm} 110 \hspace{1.5cm}$ 

Leu Met Leu Val Lys Leu Asn Ser Gln Ala Arg Leu Ser Ser Met Val 115 120 125

Lys Lys Val Arg Leu Pro Ser Arg Cys Glu Pro Pro Gly Thr Thr Cys 130 135 140

Thr Val Ser Gly Trp Gly Thr Thr Thr Ser Pro Asp Val Thr Phe Pro 145 150 155 160

Ser Asp Leu Met Cys Val Asp Val Lys Leu Ile Ser Pro Gln Asp Cys 165 170 175

Thr Lys Val Tyr Lys Asp Leu Leu Glu Asn Ser Met Leu Cys Ala Gly 180 185 190

Ile Pro Asp Ser Lys Lys Asn Ala Cys Asn Gly Asp Ser Gly Gly Pro 195 200 205

Leu Val Cys Arg Gly Thr Leu Gln Gly Leu Val Ser Trp Gly Thr Phe

210 215 220

Pro Cys Gly Gln Pro Asn Asp Pro Gly Val Tyr Thr Gln Val Cys Lys 225 230 235

Phe Thr Lys Trp Ile Asn Asp Thr Met Lys Lys His Arg  $245 \hspace{1cm} 250 \hspace{1cm}$ 

<210> 151

<211> 49

<212> PRT

<213> Homo sapiens

<400> 151-

Met Val Thr Trp Leu Tyr Arg Phe Leu Pro Thr Ser Asn Met Ala Ala 1  $\phantom{\Big|}$  10  $\phantom{\Big|}$  15

Lys Leu Arg Ser Leu Leu Pro Pro Asp Leu Arg Leu Gln Phe Trp Leu 20 25 30

His Ala Arg Leu Gln Lys Cys Phe Leu Ser Arg Gly Cys Gly Ser Tyr 35 40 45

Cys Ala Gly Ala Lys Ala Ser Pro Leu Pro Gly Lys Met Ala Met Gly  $50 \hspace{1cm} 55$ 

Leu Met Cys Gly Arg Arg Glu Leu Leu Arg Leu Leu Gln Ser Gly Arg 65 70 75 80

Arg Val His Ser Val Ala Gly Pro Ser Gln Trp Leu Gly Lys Pro Leu 85 90 90 95

Thr Thr Arg Leu Leu Phe Pro Val Ala Pro Cys Cys Cys Arg Pro His  $100 \,$   $\,$   $105 \,$   $\,$   $110 \,$ 

Tyr Leu Phe Leu Ala Ala Ser Gly Pro Arg Ser Leu Ser Thr Ser Ala 115 120 125

Ile Ser Phe Ala Glu Val Gln Val Gln Ala Pro Pro Val Val Ala Ala 130 135 140

Thr Pro Ser Pro Thr Ala Val Pro Glu Val Ala Ser Gly Glu Thr Ala 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ 

Asp Val Val Gln Thr Ala Ala Glu Gln Ser Phe Ala Glu Leu Gly Leu 165  $\phantom{\bigg|}170\phantom{\bigg|}$ 

Gly Ser Tyr Thr Pro Val Gly Leu Ile Gln Asn Leu Leu Glu Phe Met 180 185 190

His Val Asp Leu Gly Leu Pro Trp Trp Gly Ala Ile Ala Ala Cys Thr 195 200 205

Val Phe Ala Arg Cys Leu Ile Phe Pro Leu Ile Val Thr Gly Gln Arg 210 215 220

Glu Ala Ala Arg Ile His Asn His Leu Pro Glu Ile Gln Lys Phe Ser 225 230 235 240

Ser Arg Ile Arg Glu Ala Lys Leu Ala Gly Asp His Ile Glu Tyr Tyr Page 228

245 250 255

Lys Ala Ser Ser Glu Met Ala Leu Tyr Gln Lys Lys His Gly Ile Lys  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 265$ 

Leu Tyr Lys Pro Leu Ile Leu Pro Val Thr Gln Ala Pro Ile Phe Ile 275 280 285

Ser Phe Phe Ile Ala Leu Arg Glu Met Ala Asn Leu Pro Val Pro Ser 290 295 300

Leu Gln Thr Gly Gly Leu Trp Trp Phe Gln Asp Leu Thr Val Ser Asp 305 310 315 320

Pro Ile Tyr Ile Leu Pro Leu Ala Val Thr Ala Thr Met Trp Ala Val 325 330 335

Leu Glu Leu Gly Ala Glu Thr Gly Val Gln Ser Ser Asp Leu Gln Trp 340 345 350

Met Arg Asn Val Ile Arg Met Met Pro Leu Ile Thr Leu Pro Ile Thr 355 360 365

Met His Phe Pro Thr Ala Val Phe Met Tyr Trp Leu Ser Ser Asn Leu 370 380

Phe Ser Leu Val Gln Val Ser Cys Leu Arg Ile Pro Ala Val Arg Thr 385 390 395 400

Val Leu Lys Ile Pro Gln Arg Val Val His Asp Leu Asp Lys Leu Pro 405 410 415

Pro Arg Glu Gly Phe Leu Glu Ser Phe Lys Lys Gly Trp Lys Asn Ala 420 425 430

Glu Met Thr Arg Gln Leu Arg Glu Arg Glu Gln Arg Met Arg Asn Gln 435 440 445

Leu Glu Leu Ala Ala Arg Gly Pro Leu Arg Gln Thr Phe Thr His Asn 450 455 460

Pro Leu Leu Gln Pro Gly Lys Asp Asn Pro Pro Asn Ile Pro Ser Ser 465 470 475 480

Ser Ser Lys Pro Lys Ser Lys Tyr Pro Trp His Asp Thr Leu Gly 485 490 495

<210> 152

<211> 351

<212> PRT

<213> Homo sapiens

<400> 152

Met Gly Asn Ala Ala Thr Ala Lys Lys Gly Ser Glu Val Glu Ser Val 1 5 10 15

Lys Glu Phe Leu Ala Lys Ala Lys Glu Asp Phe Leu Lys Lys Trp Glu 20 25 30

Asn Pro Thr Gln Asn Asn Ala Gly Leu Glu Asp Phe Glu Arg Lys Lys Page 229

35 40 45

Thr Leu Gly Thr Gly Ser Phe Gly Arg Val Met Leu Val Lys His Lys 50 60

Ala Thr Glu Gln Tyr Tyr Ala Met Lys Ile Leu Asp Lys Gln Lys Val 65 70 80

Val Lys Leu Lys Gln Ile Glu His Thr Leu Asn Glu Lys Arg Ile Leu 85 90 95

Gln Ala Val Asn Phe Pro Phe Leu Val Arg Leu Glu Tyr Ala Phe Lys 100 105 110

Asp Asn Ser Asn Leu Tyr Met Val Met Glu Tyr Val Pro Gly Gly Glu 115 120 125

Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 130 135 140

Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 145 150 155 160

Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 170 175

His Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val 180  $$180\$ 

Lys Gly Arg Thr Trp Thr Leu Cys Gly Thr Pro Glu Tyr Leu Ala Pro 195 200 205

Glu Ile Ile Leu Ser Lys Gly Tyr Asn Lys Ala Val Asp Trp Trp Ala 210 215 220

Leu Gly Val Leu Ile Tyr Glu Met Ala Ala Gly Tyr Pro Pro Phe Phe 225 230 235 240

Ala Asp Gln Pro Ile Gln Ile Tyr Glu Lys Ile Val Ser Gly Lys Val  $245 \hspace{1cm} 250 \hspace{1cm} 255 \hspace{1cm}$ 

Arg Phe Pro Ser His Phe Ser Ser Asp Leu Lys Asp Leu Leu Arg Asn 260 265 270

Leu Leu Gln Val Asp Leu Thr Lys Arg Phe Gly Asn Leu Lys Asn Gly 275 280 285

Val Ser Asp Ile Lys Thr His Lys Trp Phe Ala Thr Thr Asp Trp Ile 290  $\phantom{\bigg|}295\phantom{\bigg|}$ 

Ala Ile Tyr Gln Arg Lys Val Glu Ala Pro Phe Ile Pro Lys Phe Arg 305 310 315 320

Gly Ser Gly Asp Thr Ser Asn Phe Asp Asp Tyr Glu Glu Glu Asp Ile 325 330 335

Arg Val Ser Ile Thr Glu Lys Cys Ala Lys Glu Phe Gly Glu Phe 340  $\phantom{-}$  345  $\phantom{-}$  350

<210> PRT <213> Homo sapiens <400> 153 Met Val Phe Arg Arg Phe Val Glu Val Gly Arg Val Ala Tyr Val Ser 1 5 10 15 Phe Gly Pro His Ala Gly Lys Leu Val Ala Ile Val Asp Val Ile Asp  $20 \hspace{1cm} 25 \hspace{1cm} 30$ Gln Asn Arg Ala Leu Val Asp Gly Bro Cys Thr Gln Val Arg Arg Gln 35 40 45Ala Met Pro Phe Lys Cys Met Gln Leu Thr Asp Phe Ile Leu Lys Phe 50 60Leu His Ser Ala His Gln Lys Tyr Val Arg Gln Ala Trp Gln Lys Ala 65 70 75 80 Asp Ile Asn Thr Lys Trp Ala Ala Thr Arg Trp Ala Lys Lys Ile Glu 85 90 95 Ala Arg Glu Arg Lys Ala Lys Met Thr Asp Phe Asp Arg Phe Lys Val 100 105 110Met Lys Ala Lys Lys Met Arg Asn Arg Ile Ile Lys Asn Glu Val Lys 115 120 125Lys Leu Gln Lys Ala Ala Leu Leu Lys Ala Ser Pro Lys Lys Ala Pro 130 135 140 Ala Ala Ala Lys Val Pro Ala Lys Lys Ile Thr Ala Ala Ser Lys 165 170 175Lys Ala Pro Ala Gln Lys Val Pro Ala Gln Lys Ala Thr Gly Gln Lys 180 185 190 Ala Ala Pro Ala Pro Lys Ala Gln Lys Gly Gln Lys Ala Pro Ala Gln 195 200 205

Lys Ala Pro Ala Pro Lys Ala Ser Gly Lys Lys Ala 210 215 220

<210> 154 <211> 492 <212> PRT <213> Homo sapiens

<400> 154

Met Ala Pro Val Gly Val Glu Lys Lys Leu Leu Leu Gly Pro Asn Gly 1 5 10 15

Pro Ala Val Ala Ala Ala Gly Asp Leu Thr Ser Glu Glu Glu Gly 20  $\phantom{-}25\phantom{+}30\phantom{+}$ 

Gln Ser Leu Trp Ser Ser Ile Leu Ser Glu Val Ser Thr Arg Ala Arg Page 231 35 40 45

Ser Lys Leu Pro Ser Gly Lys Asn Ile Leu Val Phe Gly Glu Asp Gly 50 60

Ser Gly Lys Thr Thr Leu Met Thr Lys Leu Gln Gly Ala Glu His Gly 65 70 75 80

Lys Lys Gly Arg Gly Leu Glu Tyr Leu Tyr Leu Ser Val His Asp Glu 85 90 95

Asp Arg Asp Asp His Thr Arg Cys Asn Val Trp Ile Leu Asp Gly Asp  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

Leu Tyr His Lys Gly Leu Leu Lys Phe Ala Val Ser Ala Glu Ser Leu 115 120 125

Pro Glu Thr Leu Val Ile Phe Val Ala Asp Met Ser Arg Pro Trp Thr 130 135 140

Val Met Glu Ser Leu Gln Lys Trp Ala Ser Val Leu Arg Glu His Ile 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ 

Asp Lys Met Lys Ile Pro Pro Glu Lys Met Arg Glu Leu Glu Arg Lys  $165 \hspace{1.5cm} 170 \hspace{1.5cm} 175 \hspace{1.5cm}$ 

Phe Val Lys Asp Phe Gln Asp Tyr Met Glu Pro Glu Glu Gly Cys Gln 180 185 190

Gly Ser Pro Gln Arg Arg Gly Pro Leu Thr Ser Gly Ser Asp Glu Glu 195 200 . 205

Asn Val Ala Leu Pro Leu Gly Asp Asn Val Leu Thr His Asn Leu Gly 210 215 220

Glu Lys Glu His Asp Tyr Arg Asp Glu His Leu Asp Phe Ile Gln Ser 245 250 255

His Leu Arg Arg Phe Cys Leu Gln Tyr Gly Ala Ala Leu Ile Tyr Thr 260 265 270

Ser Val Lys Glu Glu Lys Asn Leu Asp Leu Leu Tyr Lys Tyr Ile Val 275 280 285

His Lys Thr Tyr Gly Phe His Phe Thr Thr Pro Ala Leu Val Val Glu 290 295 300

Lys Asp Ala Val Phe Ile Pro Ala Gly Trp Asp Asn Glu Lys Lys Ile 305 310 315 320

Ala Ile Leu His Glu Asn Phe Thr Thr Val Lys Pro Glu Asp Ala Tyr 325 330 335

Glu Asp Phe Ile Val Lys Pro Pro Val Arg Lys Leu Val His Asp Lys 340 345 350

Glu Leu Ala Ala Glu Asp Glu Gln Val Phe Leu Met Lys Gln Gln Ser 355 360 365

Ala Arg Gly Pro Ser Gly Ser Pro Arg Thr Gln Gly Arg Gly Gly Pro 385 390 395 400

Ala Ser Val Pro Ser Ser Ser Pro Gly Thr Ser Val Lys Lys Pro Asp  $405 \hspace{1.5cm} 410 \hspace{1.5cm} 415 \hspace{1.5cm}$ 

Pro Asn Ile Lys Asn Asn Ala Ala Ser Glu Gly Val Leu Ala Ser Phe  $420 \hspace{1.5cm} 425 \hspace{1.5cm} 430$ 

Phe Asn Ser Leu Leu Ser Lys Lys Thr Gly Ser Pro Gly Ser Pro Gly 435 440 445

Ala Gly Gly Val Gln Ser Thr Ala Lys Lys Ser Gly Gln Lys Thr Val  $_{\rm 450}$ 

Leu Ser Asn Val Glu Glu Leu Asp Arg Met Thr Arg Lys Pro Asp 465 470 475 480

Ser Met Val Thr Asn Ser Ser Thr Glu Asn Glu Ala 485 490

(210> 155

<211> 2230

<212> PRT

<213> Homo sapiens

<400> 155

Met Phe Lys Lys Leu Lys Gln Lys Ile Ser Glu Glu Gln Gln Gln Leu 1 5 10 15

Gln Gln Ala Leu Ala Pro Ala Gln Ala Ser Ser Asn Ser Ser Thr Pro 20 25 30

Thr Arg Met Arg Ser Arg Thr Ser Ser Phe Thr Glu Gln Leu Asp Glu 35 40 45

Gly Thr Pro Asn Arg Glu Ser Gly Asp Thr Gln Ser Phe Ala Gln Lys 50 60

Leu Gln Leu Arg Val Pro Ser Val Glu Ser Leu Phe Arg Ser Pro Ile 65 . 70 80

Lys Glu Ser Leu Phe Arg Ser Ser Ser Lys Glu Ser Leu Val Arg Thr 85 90 95

Ser Ser Arg Glu Ser Leu Asn Arg Leu Asp Leu Asp Ser Ser Thr Ala 100 105 110

Ser Phe Asp Pro Pro Ser Asp Met Asp Ser Glu Ala Glu Asp Leu Val 115 120 125

Gly Asn Ser Asp Ser Leu Asn Lys Glu Gln Leu Ile Gln Arg Leu Arg 130 135 140 Arg Met Glu Arg Ser Leu Ser Ser Tyr Arg Gly Lys Tyr Ser Glu Leu 145 150 155 160

Val Thr Ala Tyr Gln Met Leu Gln Arg Glu Lys Lys Lys Leu Gln Gly
165 170 175

Ile Leu Ser Gln Ser Gln Asp Lys Ser Leu Arg Arg Ile Ala Glu Leu 180 185 190

Arg Glu Glu Leu Gln Met Asp Gln Gln Ala Lys Lys His Leu Gln Glu 195 200 205

Glu Phe Asp Ala Ser Leu Glu Glu Lys Asp Gln Tyr Ile Ser Val Leu 210 220

Gln Thr Gln Val Ser Leu Leu Lys Gln Arg Leu Arg Asn Gly Pro Met 225 230 235 240

Asn Val Asp Val Leu Lys Pro Leu Pro Gln Leu Glu Pro Gln Ala Glu 245 250 250

Val Phe Thr Lys Glu Glu Asn Pro Glu Ser Asp Gly Glu Pro Val Val 260 265 270

Glu Asp Gly Thr Ser Val Lys Thr Leu Glu Thr Leu Gln Gln Arg Val 275 280 285

Lys Arg Gln Glu Asn Leu Leu Lys Arg Cys Lys Glu Thr Ile Gln Ser 290

His Lys Glu Gln Cys Thr Leu Leu Thr Ser Glu Lys Glu Ala Leu Gln 305 310 315 320

Glu Gln Leu Asp Glu Arg Leu Gln Glu Leu Glu Lys Ile Lys Asp Leu 325  $\phantom{\bigg|}330\phantom{\bigg|}$  330  $\phantom{\bigg|}335\phantom{\bigg|}$ 

His Met Ala Glu Lys Thr Lys Leu Ile Thr Gln Leu Arg Asp Ala Lys  $340 \hspace{1.5cm} 345 \hspace{1.5cm} 350 \hspace{1.5cm}$ 

Asn Leu Ile Glu Gln Leu Glu Gln Asp Lys Gly Met Val Ile Ala Glu 355  $\phantom{\bigg|}360\phantom{\bigg|}$ 

Thr Lys Arg Gln Met His Glu Thr Leu Glu Met Lys Glu Glu Glu Ile 370 380

Ala Gln Leu Arg Ser Arg Ile Lys Gln Met Thr Thr Gln Gly Glu Glu 385 390 395 400

Leu Arg Glu Gln Lys Glu Lys Ser Glu Arg Ala Phe Glu Glu Leu 405 410 415

Glu Lys Ala Leu Ser Thr Ala Gln Lys Thr Glu Glu Ala Arg Arg Lys 420 425 430

Leu Lys Ala Glu Met Asp Glu Gln Ile Lys Thr Ile Glu Lys Thr Ser  $435 \hspace{1.5cm} 440 \hspace{1.5cm} 445$ 

Glu Glu Glu Arg Ile Ser Leu Gln Gln Glu Leu Ser Arg Val Lys Gln 450 455 460

Glu Val Val Asp Val Met Lys Lys Ser Ser Glu Glu Gln Ile Ala Lys 465 470 475 480

Leu Gln Lys Leu His Glu Lys Glu Leu Ala Arg Lys Glu Gln Glu Leu 485 490 495

Thr Lys Lys Leu Gln Thr Arg Glu Arg Glu Phe Gln Glu Gln Met Lys 500 505 510

Val Ala Leu Glu Lys Ser Gln Ser Glu Tyr Leu Lys Ile Ser Gln Glu 515 520 525

Lys Glu Gln Gln Glu Ser Leu Ala Leu Glu Glu Leu Glu Leu Gln Lys 530 535 540

Lys Ala Ile Leu Thr Glu Ser Glu Asn Lys Leu Arg Asp Leu Gln Gln 545 550 555 560

Glu Ala Glu Thr Tyr Arg Thr Arg Ile Leu Glu Leu Glu Ser Ser Leu 565 570 575

Glu Lys Ser Leu Gln Glu Asn Lys Asn Gln Ser Lys Asp Leu Ala Val580  $\phantom{0}585$   $\phantom{0}595$ 

His Leu Glu Ala Glu Lys Asn Lys His Asn Lys Glu Ile Thr Val Met  $595 \hspace{1.5cm} 600 \hspace{1.5cm} 605$ 

Val Glu Lys His Lys Thr Glu Leu Glu Ser Leu Lys His Gln Gln Asp 610 615 620

Ala Leu Trp Thr Glu Lys Leu Gln Val Leu Lys Gln Gln Tyr Gln Thr 625 630 635 640

Glu Met Glu Lys Leu Arg Glu Lys Cys Glu Gln Glu Lys Glu Thr Leu 645 650 655

Leu Lys Asp Lys Glu Ile Ile Phe Gln Ala His Ile Glu Glu Met Asn 660 665 670

Glu Lys Thr Leu Glu Lys Leu Asp Val Lys Gln Thr Glu Leu Glu Ser 675 680 685

Leu Ser Ser Glu Leu Ser Glu Val Leu Lys Ala Arg His Lys Leu Glu 690 695 700

Glu Glu Leu Ser Val Leu Lys Asp Gln Thr Asp Lys Met Lys Gln Glu 705 710 715 720

Leu Glu Ala Lys Met Asp Glu Gln Lys Asn His His Gln Gln Gln Val $725 \hspace{1cm} 730 \hspace{1cm} 735$ 

Asp Ser Ile Ile Lys Glu His Glu Val Ser Ile Gln Arg Thr Glu Lys  $740 \hspace{1cm} 745 \hspace{1cm} 750$ 

Ala Leu Lys Asp Gln Ile Asn Gln Leu Glu Leu Leu Leu Lys Glu Arg 755 760 765

Asp Lys His Leu Lys Glu His Gln Ala His Val Glu Asn Leu Glu Ala 770 775 780

Asp Ile Lys Arg Ser Glu Gly Glu Leu Gln Gln Ala Ser Ala Lys Leu 785 790 795 800

Asp Val Phe Gln Ser Tyr Gln Ser Ala Thr His Glu Gln Thr Lys Ala 805 810 815

Tyr Glu Glu Gln Leu Ala Gln Leu Gln Gln Lys Leu Leu Asp Leu Glu 820 825 830

Thr Glu Arg Ile Leu Leu Thr Lys Gln Val Ala Glu Val Glu Ala Gln 835 840 845

Lys Lys Asp Val Cys Thr Glu Leu Asp Ala His Lys Ile Gln Val Gln 850 855 860

Asp Leu Met Gln Gln Leu Glu Lys Gln Asn Ser Glu Met Glu Gln Lys 865 870 875 880

Val Lys Ser Leu Thr Gln Val Tyr Glu Ser Lys Leu Glu Asp Gly Asn 885 890 895

Lys Glu Gln Glu Gln. Thr Lys Gln Ile Leu Val Glu Lys Glu Asn Met 900 910

Ile Leu Gln Met Arg Glu Gly Gln Lys Lys Glu Ile Glu Ile Leu Thr 915 920 925

Gln Lys Leu Ser Ala Lys Glu Asp Ser Ile His Ile Leu Asn Glu Glu 930  $\phantom{000}\cdot\phantom{0}935\phantom{0}$  940

Tyr Glu Thr Lys Phe Lys Asn Gln Glu Lys Lys Met Glu Lys Val Lys 945 950 955 960

Gln Lys Ala Lys Glu Met Gln Glu Thr Leu Lys Lys Lys Leu Leu Asp 965 970 975

Gln Glu Ala Lys Leu Lys Lys Glu Leu Glu Asn Thr Ala Leu Glu Leu 980 985 990

Ser Gln Lys Glu Lys Gln Phe Asn Ala Lys Met Leu Glu Met Ala Gln 995 1000 1005

Ala Asn Ser Ala Gly Ile Ser Asp Ala Val Ser Arg Leu Glu Thr 1010 1015 1020

Asn Gln Lys Glu Gln Ile Glu Ser Leu Thr Glu Val His Arg Arg 1025 1030 1035

Glu Leu Asn Asp Val Ile Ser Ile Trp Glu Lys Lys Leu Asn Gln  $1040 \,$  1045  $\,$  1050

Gln Ala Glu Glu Leu Gln Glu Ile His Glu Ile Gln Leu Gln Glu 1055 1060 1065

Lys Glu Gln Glu Val Ala Glu Leu Lys Gln Lys Ile Leu Leu Phe 1070  $\,\,$  1075  $\,\,$  1080

Gly Cys Glu Lys Glu Glu Met Asn Lys Glu Ile Thr Trp Leu Lys Page 236 1085 1090 1095

Glu Glu Gly Val Lys Gln Asp Thr Thr Leu Asn Glu Leu Gln Glu 1100 1105 1110

- Gln Leu Lys Gln Lys Ser Ala His Val Asn Ser Leu Ala Gln Asp 1115 1120 1125
- Glu Thr Lys Leu Lys Ala His Leu Glu Lys Leu Glu Val Asp Leu 1130 1140
- Asn Lys Ser Leu Lys Glu Asn Thr Phe Leu Gln Glu Gln Leu Val 1145 1150 1155
- Glu Leu Lys Met Leu Ala Glu Glu Asp Lys Arg Lys Val Ser Glu 1160 1165 1170
- Leu Thr Ser Lys Leu Lys Thr Thr Asp Glu Glu Phe Gln Ser Leu 1175 1180 1185
- Lys Ser Ser His Glu Lys Ser Asn Lys Ser Leu Glu Asp Lys Ser 1190 1195 1200
- Leu Glu Phe Lys Lys Leu Ser Glu Glu Leu Ala Ile Gln Leu Asp 1205 1210 1215
- Ile Cys Cys Lys Lys Thr Glu Ala Leu Leu Glu Ala Lys Thr Asn 1220 1225 1230
- Glu Leu Ile Asn Ile Ser Ser Ser Lys Thr Asn Ala Ile Leu Ser 1235 1240 1245
- Arg Ile Ser His Cys Gln His Arg Thr Thr Lys Val Lys Glu Ala 1250 1255 1260
- Leu Leu Ile Lys Thr Cys Thr Val Ser Glu Leu Glu Ala Gln Leu 1265 1270 1275
- Arg Gln Leu Thr Glu Glu Gln Asn Thr Leu Asn Ile Ser Phe Gln 1280 1285 1290
- Gln Ala Thr His Gln Leu Glu Glu Lys Glu Asn Gln Ile Lys Ser 1295 1300 1305
- Met Lys Ala Asp Ile Glu Ser Leu Val Thr Glu Lys Glu Ala Leu 1310 1315 1320
- Gln Lys Glu Gly Gly Asn Gln Gln Gln Ala Ala Ser Glu Lys Glu 1325 1330 1335
- Ser Cys Ile Thr Gln Leu Lys Lys Glu Leu Ser Glu Asn Ile Asn 1340 1350
- Ala Val Thr Leu Met Lys Glu Glu Leu Lys Glu Lys Lys Val Glu 1355 1360 1365
- Ile Ser Ser Leu Ser Lys Gln Leu Thr Asp Leu Asn Val Gln Leu 1370 1375 1380

Gin Asn	Ser	Ile	Ser	Leu	Ser	Glu	Lys	Glu	ATa	ATA	тте	Ser	ser
1385					1390		•			1395			

- Leu Arg Lys Gln Tyr Asp Glu Glu Lys Cys Glu Leu Leu Asp Gln 1400 1405 1410
- Val Gln Asp Leu Ser Phe Lys Val Asp Thr Leu Ser Lys Glu Lys 1415 1420 1425
- Ile Ser Ala Leu Glu Gln Val Asp Asp Trp Ser Asn Lys Phe Ser 1430 1435 1440
- Glu Trp Lys Lys Lys Ala Gln Ser Arg Phe Thr Gln His Gln Asn 1445 \$1450\$
- Thr Val Lys Glu Leu Gln Ile Gln Leu Glu Leu Lys Ser Lys Glu 1460 1465 1470
- Ala Tyr Glu Lys Asp Glu Gln Ile Asn Leu Leu Lys Glu Glu Leu 1475 1480 1485
- Asp Gln Gln Asn Lys Arg Phe Asp Cys Leu Lys Gly Glu Met Glu 1490 1495 1500
- Asp Asp Lys Ser Lys Met Glu Lys Lys Glu Ser Asn Leu Glu Thr  $1505 \\ \hspace*{1.5cm} 1510 \\ \hspace*{1.5cm} \hspace*{1.5cm} 1515 \\ \hspace*{1.5cm} \hspace*{1.5cm}$
- Glu Leu Lys Ser Gln Thr Ala Arg Ile Met Glu Leu Glu Asp His 1520 1530
- Ile Thr Gln Lys Thr Ile Glu Ile Glu Ser Leu Asn Glu Val Leu 1535 1540 1545
- Lys Asn Tyr Asn Gln Gln Lys Asp Ile Glu His Lys Glu Leu Val 1550  $\phantom{0}$  1555
- Gln Lys Leu Gln His Phe Gln Glu Leu Gly Glu Glu Lys Asp Asn 1565 1570 1575
- Arg Val Lys Glu Ala Glu Glu Lys Ile Leu Thr Leu Glu Asn Gln 1580  $$1585\ \ \ ]$
- Val Tyr Ser Met Lys Ala Glu Leu Glu Thr Lys Lys Lys Glu Leu 1595 1600 1605
- Glu His Val Asn Leu Ser Val Lys Ser Lys Glu Glu Glu Leu Lys  $1610 \hspace{1.5cm} 1615 \hspace{1.5cm} 1620 \hspace{1.5cm}$
- Ala Leu Glu Asp Arg Leu Glu Ser Glu Ser Ala Ala Lys Leu Ala 1625 1630 1635
- Glu Leu Lys Arg Lys Ala Glu Gln Lys Ile Ala Ala Ile Lys Lys 1640 1645 1650
- Gln Leu Leu Ser Gln Met Glu Glu Lys Glu Glu Gln Tyr Lys Lys 1655 1660 1665
- Gly Thr Glu Ser His Leu Ser Glu Leu Asn Thr Lys Leu Gln Glu 1670 1675 1680

Arg Glu Arg Glu Val His Ile Leu Glu Glu Lys Leu Lys Ser Val 1685 1690 1695

Glu Ser Ser Gln Ser Glu Thr Leu Ile Val Pro Arg Ser Ala Lys  $1700 \hspace{1.5cm} 1705 \hspace{1.5cm} 1710$ 

Asn Val Ala Ala Tyr Thr Glu Glu Glu Ala Asp Ser Gln Gly 1715 1720 1725

Cys Val Gln Lys Thr Tyr Glu Glu Lys Ile Ser Val Leu Gln Arg 1730 1735 1740

Asn Leu Thr Glu Lys Glu Lys Leu Leu Gln Arg Val Gly Gln Glu 1745 1750 1755

Lys Glu Glu Thr Val Ser Ser His Phe Glu Met Arg Cys Gln Tyr 1760 1765 1770

Gln Glu Arg Leu Ile Lys Leu Glu His Ala Glu Ala Lys Gln His 1775 1780 1785

Glu Asp Gln Ser Met Ile Gly His Leu Gln Glu Glu Leu Glu Glu 1790 1795 1800

Lys Asn Lys Lys Tyr Ser Leu Ile Val Ala Gln His Val Glu Lys 1805 1810 1815

Glu Gly Gly Lys Asn Asn Ile Gln Ala Lys Gln Asn Leu Glu Asn 1820 1830

Val Phe Asp Asp Val Gln Lys Thr Leu Gln Glu Lys Glu Leu Thr 1835 1840 1845

Cys Gln Ile Leu Glu Gln Lys Ile Lys Glu Leu Asp Ser Cys Leu 1850 1860

Val Arg Gln Lys Glu Val His Arg Val Glu Met Glu Glu Leu Thr 1865 1870 1875

Ser Lys Tyr Glu Lys Leu Gln Ala Leu Gln Gln Met Asp Gly Arg 1880 1890

Asn Lys Pro Thr Glu Leu Leu Glu Glu Asn Thr Glu Glu Lys Ser 1895 1900 1905

Lys Ser His Leu Val Gln Pro Lys Leu Leu Ser Asn Met Glu Ala 1910 1915 1920

Gln His Asn Asp Leu Glu Phe Lys Leu Ala Gly Ala Glu Arg Glu 1925 1930 1935

Lys Gln Lys Leu Gly Lys Glu Ile Val Arg Leu Gln Lys Asp Leu 1940 1945 1950

Arg Met Leu Arg Lys Glu His Gln Gln Glu Leu Glu Ile Leu Lys 1955 1960 1965

Lys Glu Tyr Asp Gln Glu Arg Glu Glu Lys Ile Lys Gln Glu Gln 1970 1975 1980

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Glu Asp Leu Glu Leu Lys His Asn Ser Thr Leu Lys Gln Leu Met 1985 1990 1995 Arg Glu Phe Asn Thr Gln Leu Ala Gln Lys Glu Gln Glu Leu Glu 2000 2005 2010 Met Thr Ile Lys Glu Thr Ile Asn Lys Ala Glu Glu Val Glu Ala 2015 2020 2025 Glu Leu Leu Glu Ser His Gln Glu Glu Thr Asn Gln Leu Leu Lys 2030 2040 Lys Ile Ala Glu Lys Asp Asp Asp Leu Lys Arg Thr Ala Lys Arg 2045 2055 .Tyr Glu Glu Ile Leu Asp Ala Arg Glu Glu Met Thr Ala Lys  $2060 \hspace{1.5cm} 2065 \hspace{1.5cm} 2070$ Val Arg Asp Leu Gln Thr Gln Leu Glu Glu Leu Gln Lys Lys Tyr 2075 2080 2085 Gln Gln Lys Leu Glu Gln Glu Glu Asn Pro Gly Asn Asp Asn Val 2090 2095 2100 Thr Ile Met Glu Leu Gln Thr Gln Leu Ala Gln Lys Thr Thr Leu 2105 2110 2115 Ile Ser Asp Ser Lys Leu Lys Glu Glu Glu Phe Arg Glu Gln Ile 2120 2125 2130 His Asn Leu Glu Asp Arg Leu Lys Lys Tyr Glu Lys Asn Val Tyr 2135 2140 2145 Ala Thr Thr Val Gly Thr Pro Tyr Lys Gly Gly Asn Leu Tyr His 2150 2160 Thr Asp Val Ser Leu Phe Gly Glu Pro Thr Glu Phe Glu Tyr Leu 2165 2170 2175 Met Ala Lys Val Ile Thr Thr Val Leu Lys Phe Pro Asp Asp Gln 2195 2200 2205 Thr Gln Lys Ile Leu Glu Arg Glu Asp Ala Arg Leu Met Phe Thr 2210 2215 2220

Ser Pro Arg Ser Gly Ile Phe 2225 2230

<210> 156 <211> 719 <212> PRT <213> Homo sapiens

<400> 156

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Leu Glu Ala Arg Phe Thr Gly Val Gly Val Ser Lys Gly Pro Leu Asn 20 25 30 .

Ser Glu Ser Ser Asn Gln Ser Leu Cys Ser Val Gly Ser Leu Ser Asp 35 40 45

Lys Glu Val Glu Thr Pro Glu Lys Lys Gln Asn Asp Gln Arg Asn Arg 50 60

Lys Arg Lys Ala Glu Pro Tyr Glu Thr Ser Gln Gly Lys Gly Thr Pro 65 70 75 80

Arg Gly His Lys Ile Ser Asp Tyr Phe Glu Arg Arg Val Glu Gln Pro 85 90 95

Leu Tyr Gly Leu Asp Gly Ser Ala Ala Lys Glu Ala Thr Glu Glu Gln  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110 \hspace{1.5cm}$ 

Ser Ala Leu Pro Thr Leu Met Ser Val Met Leu Ala Lys Pro Arg Leu 115 120 125

Val Ser Ala Gln Gln Asn Ser Pro Ser Ser Thr Gly Ser Gly Asn Thr 145 150 150 160

Glu His Ser Cys Ser Ser Gln Lys Gln Ile Ser Ile Gln His Arg Gln 165 170 175

Thr Gln Ser Asp Leu Thr Ile Glu Lys Ile Ser Ala Leu Glu Asn Ser 180 185 190

Lys Asn Ser Asp Leu Glu Lys Lys Glu Gly Arg Ile Asp Asp Leu Leu 195 200 205

Arg Ala Asn Cys Asp Leu Arg Arg Gln Ile Asp Glu Gln Gln Lys Met 210 215 220

Leu Glu Lys Tyr Lys Glu Arg Leu Asn Arg Cys Val Thr Met Ser Lys 225 230 235

Lys Leu Leu Ile Glu Lys Ser Lys Gln Glu Lys Met Ala Cys Arg Asp  $245 \hspace{1cm} 250 \hspace{1cm} 250 \hspace{1cm} 255 \hspace{1cm}$ 

Lys Ser Met Gln Asp Arg Leu Arg Leu Gly His Phe Thr Thr Val Arg 260 265 270

His Gly Ala Ser Phe Thr Glu Gln Trp Thr Asp Gly Tyr Ala Phe Gln 275 280 285

Asn Leu Ile Lys Gln Gln Glu Arg Ile Asn Ser Gln Arg Glu Glu Ile 290 295 300

Glu Arg Gln Arg Lys Met Leu Ala Lys Arg Lys Pro Pro Ala Met Gly 305 310 . 315 920

Gln Ala Pro Pro Ala Thr Asn Glu Gln Lys Gln Arg Lys Ser Lys Thr Page 241

325 330 335

Asn Gly Ala Glu Asn Glu Thr Leu Thr Leu Ala Glu Tyr His Glu Gln 340 345 350

Glu Glu Ile Phe Lys Leu Arg Leu Gly His Leu Lys Lys Glu Glu Ala 355 360 365

Glu Ile Gln Ala Glu Leu Glu Arg Leu Glu Arg Val Arg Asn Leu His 370 380

Ile Arg Glu Leu Lys Arg Ile His Asn Glu Asp Asn Ser Gln Phe Lys 385 390 395 400

Asp His Pro Thr Leu Asn Asp Arg Tyr Leu Leu Leu His Leu Leu Gly 405 410 415

Arg Gly Gly Phe Ser Glu Val Tyr Lys Ala Phe Asp Leu Thr Glu Gln 420 425 430

Arg Tyr Val Ala Val Lys Ile His Gln Leu Asn Lys Asn Trp Arg Asp 435 440 445

Glu Lys Lys Glu Asn Tyr His Lys His Ala Cys Arg Glu Tyr Arg Ile 450 455 460

His Lys Glu Leu Asp His Pro Arg Ile Val Lys Leu Tyr Asp Tyr Phe 465 470 475 480

Ser Leu Asp Thr Asp Ser Phe Cys Thr Val Leu Glu Tyr Cys Glu Gly 485 490 495

Asn Asp Leu Asp Phe Tyr Leu Lys Gln His Lys Leu Ile Ser Glu Lys 500 505 510

Glu Ala Arg Ser Ile Ile Met Gln Ile Val Asn Ala Leu Lys Tyr Leu 515 520 525

Asn Glu Ile Lys Pro Pro Ile Ile His Tyr Asp Leu Lys Pro Gly Asn 530 540

Ile Leu Leu Val Asn Gly Thr Ala Cys Gly Glu Ile Lys Ile Thr Asp 545 550 555 560

Phe Gly Leu Ser Lys Ile Met Asp Asp Asp Ser Tyr Asn Ser Val Asp 565 570 575

Gly Met Glu Leu Thr Ser Gln Gly Ala Gly Thr Tyr Trp Tyr Leu Pro 580 585 590

Pro Glu Cys Phe Val Val Gly Lys Glu Pro Pro Lys Ile Ser Asn Lys 595 600 605

Val Asp Val Trp Ser Val Gly Val Ile Phe Tyr Gln Cys Leu Tyr Gly 610 620

Arg Lys Pro Phe Gly His Asn Gln Ser Gln Gln Asp Ile Leu Gln Glu 625 630 635 640

Asn Thr Ile Leu Lys Ala Thr Glu Val Gln Phe Pro Pro Lys Pro Val 645 650 655

Val Thr Pro Glu Ala Lys Ala Phe Ile Arg Arg Cys Leu Ala Tyr Arg 660 665 670

Lys Glu Asp Arg Ile Asp Val Gln Gln Leu Ala Cys Asp Pro Tyr Leu 675 680 685

Leu Pro His Ile Arg Lys Ser Val Ser Thr Ser Ser Pro Ala Gly Ala  $690 \hspace{1.5cm} 695 \hspace{1.5cm} 700$ 

Ala Ile Ala Ser Thr Ser Gly Ala Ser Asn Asn Ser Ser Ser Asn 705 710 715

<210> 157

<211> 1976

<212> PRT

<213> Homo sapiens

<400> 157

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Asp Arg Ala Val Ile Tyr Asn Pro Ala Thr Gln Ala Asp Trp Thr Ala  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Lys Lys Leu Val Trp Ile Pro Ser Glu Arg His Gly Phe Glu Ala Ala  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Ser Ile Lys Glu Glu Arg Gly Asp Glu Val Met Val Glu Leu Ala Glu 50 60

Asn Gly Lys Lys Ala Met Val Asn Lys Asp Asp Ile Gln Lys Met Asn 65 70 75 80

Pro Pro Lys Phe Ser Lys Val Glu Asp Met Ala Glu Leu Thr Cys Leu 85 90 95

Asn Glu Ala Ser Val Leu His Asn Leu Lys Asp Arg Tyr Tyr Ser Gly 100 105 110

Leu Ile Tyr Thr Tyr Ser Gly Leu Phe Cys Val Val Ile Asn Pro Tyr 115 120 125

Lys Asn Leu Pro Ile Tyr Ser Glu Asn Ile Ile Glu Met Tyr Arg Gly 130 135 140

Lys Lys Arg His Glu Met Pro Pro His Ile Tyr Ala Ile Ser Glu Ser 145 150 155 160

Ala Tyr Arg Cys Met Leu Gln Asp Arg Glu Asp Gln Ser Ile Leu Cys 165 170 175

Thr Gly Glu Ser Gly Ala Gly Lys Thr Glu Asn Thr Lys Lys Val Ile  $180 \hspace{1cm} 185 \hspace{1cm} 190$ 

Gln Tyr Leu Ala His Val Ala Ser Ser His Lys Gly Arg Lys Asp His 195 200 205

- Asn Ile Pro Gly Glu Leu Glu Arg Gln Leu Leu Gln Ala Asn Pro Ile 210 215 220
- Leu Glu Ser Phe Gly Asn Ala Lys Thr Val Lys Asn Asp Asn Ser Ser 225 230 230 235
- Arg Phe Gly Lys Phe Ile Arg Ile Asn Phe Asp Val Thr Gly Tyr Ile 245 250 255
- Val Gly Ala Asn Ile Glu Thr Tyr Leu Leu Glu Lys Ser Arg Ala Val 260 265 270
- Arg Gln Ala Lys Asp Glu Arg Thr Phe His Ile Phe Tyr Gln Leu Leu 275 280 285
- Ser Gly Ala Gly Glu His Leu Lys Ser Asp Leu Leu Glu Gly Phe 290 295 300
- Asn Asn Tyr Arg Phe Leu Ser Asn Gly Tyr Ile Pro Ile Pro Gly Gln 305 310 315 320
- Gln Asp Lys Asp Asn Phe Gln Glu Thr Met Glu Ala Met His Ile Met 325 330 335
- Gly Phe Ser His Glu Glu Ile Leu Ser Met Leu Lys Val Val Ser Ser 340 345 350
- Val Leu Gln Phe Gly Asn Ile Ser Phe Lys Lys Glu Arg Asn Thr Asp 355 360 365
- Gln Ala Ser Met Pro Glu Asn Thr Val Ala Gln Lys Leu Cys His Leu 370 375 380
- Leu Gly Met Asn Val Met Glu Phe Thr Arg Ala Ile Leu Thr Pro Arg 385 390 395 400
- Ala Asp Phe Ala Val Glu Ala Leu Ala Lys Ala Thr Tyr Glu Arg Leu 420 425 430
- Phe Arg Trp Leu Val His Arg Ile Asn Lys Ala Leu Asp Arg Thr Lys 435 440 445
- Arg Gln Gly Ala Ser Phe Ile Gly Ile Leu Asp Ile Ala Gly Phe Glu 450 460
- Ile Phe Glu Leu Asn Ser Phe Glu Gln Leu Cys Ile Asn Tyr Thr Asn 465  $\cdot$  470  $\cdot$  475  $\cdot$  480
- Glu Lys Leu Gln Gln Leu Phe Asn His Thr Met Phe Ile Leu Glu Gln 485 490 495
- Glu Glu Tyr Gln Arg Glu Gly Ile Glu Trp Asn Phe Ile Asp Phe Gly 500 505 510
- Leu Asp Leu Gln Pro Cys Ile Asp Leu Ile Glu Arg Pro Ala Asn Pro 515 520 525

Pro Gly Val Leu Ala Leu Leu Asp Glu Glu Cys Trp Phe Pro Lys Ala 530 540

Thr Asp Lys Thr Phe Val Glu Lys Leu Val Gln Glu Gln Gly Ser His 545 550 555 560

Ser Lys Phe Gln Lys Pro Arg Gln Leu Lys Asp Lys Ala Asp Phe Cys 565 570 575

Ile Ile His Tyr Ala Gly Lys Val Asp Tyr Lys Ala Asp Glu Trp Leu  $580 \hspace{1.5cm} 595 \hspace{1.5cm} 595$ 

Met Lys Asn Met Asp Pro Leu Asn Asp Asn Val Ala Thr Leu Leu His 595 600 605

Gln Ser, Ser Asp Arg Phe Val Ala Glu Leu Trp Lys Àsp Val Asp Arg 610 620

Ile Val Gly Leu Asp Gln Val Thr Gly Met Thr Glu Thr Ala Phe Gly 625 630 635 640

Ser Ala Tyr Lys Thr Lys Lys Gly Met Phe Arg Thr Val Gly Gln Leu 645 650 655

Tyr Lys Glu Ser Leu Thr Lys Leu Met Ala Thr Leu Arg Asn Thr Asn  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 665$ 

Pro Asn Phe Val Arg Cys Ile Ile Pro Asn His Glu Lys Arg Ala Gly 675 680 685

Lys Leu Asp Pro His Leu Val Leu Asp Gln Leu Arg Cys Asn Gly Val  $690 \hspace{1cm} 695 \hspace{1cm} 700 \hspace{1cm}$ 

Leu Glu Gly Ile Arg Ile Cys Arg Gln Gly Phe Pro Asn Arg Ile Val 705 710 715 720

Phe Gln Glu Phe Arg Gln Arg Tyr Glu Ile Leu Thr Pro Asn Ala Ile 725 730 735

Pro Lys Gly Phe Met Asp Gly Lys Gln Ala Cys Glu Arg Met Ile Arg 740 745 750

Ala Leu Glu Leu Asp Pro Asn Leu Tyr Arg Ile Gly Gln Ser Lys Ile 755 760 765

Phe Phe Arg Ala Gly Val Leu Ala His Leu Glu Glu Glu Arg Asp Leu 770 780

Lys Ile Thr Asp Ile Ile Ile Phe Phe Gln Ala Val Cys Arg Gly Cys 785 790 795 800

Leu Ala Arg Lys Ala Phe Ala Lys Lys Gln Gln Gln Leu Ser Ala Leu 805 810 815

Lys Val Leu Gln Arg Asn Cys Ala Ala Tyr Leu Lys Leu Arg His Trp 820 825 830

Gln Trp Trp Arg Val Phe Thr Lys Val Lys Pro Leu Gln Val Thr 835 840 845

Page 245

Arg Gln Glu Glu Leu Gln Ala Lys Asp Glu Glu Leu Lys Val 850 855 860

Lys Glu Lys Gln Thr Lys Val Glu Gly Glu Leu Glu Glu Met Glu Arg 865 870 870 885

Lys His Gln Gln Leu Leu Glu Glu Lys Asn Ile Leu Ala Glu Gln Leu 885 890 895

Gln Ala Glu Thr Glu Leu Phe Ala Glu Ala Glu Glu Met Arg Ala Arg 900 905 910

Leu Ala Ala Lys Lys Gln Glu Leu Glu Glu Ile Leu His Asp Leu Glu 915 920 925

Ser Arg Val Glu Glu Glu Glu Glu Arg Asn Gln Ile Leu Gln Asn Glu 930 935 940

Lys Lys Lys Met Gln Ala His Ile Gln Asp Leu Glu Glu Gln Leu Asp 945 950 955 960

Glu Glu Glu Gly Ala Arg Gln Lys Leu Gln Leu Glu Lys Val Thr Ala 965 970 975

Glu Ala Lys Ile Lys Lys Met Glu Glu Glu Ile Leu Leu Glu Asp 980 985 990

Gln Asn Ser Lys Phe Ile Lys Glu Lys Lys Leu Met Glu Asp Arg Ile 995 1000 1005

Ala Glu Cys Ser Ser Gln Leu Ala Glu Glu Glu Glu Lys Ala Lys 1010 1015 1020

Asn Leu Ala Lys Ile Arg Asn Lys Gln Glu Val Met Ile Ser Asp 1025 1030 1035

Leu Glu Glu Arg Leu Lys Lys Glu Glu Lys Thr Arg Gln Glu Leu 1040 1050 1055

Glu Lys Ala Lys Arg Lys Leu Asp Gly Glu Thr Thr Asp Leu Gln 1055  $1060\,$  1065

Asp Gln Ile Ala Glu Leu Gln Ala Gln Ile Asp Glu Leu Lys Leu 1070 1075 1080

Gln Leu Ala Lys Lys Glu Glu Glu Leu Gln Gly Ala Leu Ala Arg 1085 1090 1095

Gly Asp Asp Glu Thr Leu His Lys Asn Asn Ala Leu Lys Val Val 1100  $$1105\$ 

Arg Glu Leu Gln Ala Gln Ile Ala Glu Leu Gln Glu Asp Phe Glu 1115 1120 1125

Ser Glu Lys Ala Ser Arg Asn Lys Ala Glu Lys Gln Lys Arg Asp 1130 1135 1140

Leu Ser Glu Glu Leu Glu Ala Leu Lys Thr Glu Leu Glu Asp Thr

	1145					1150					1155			
Leu	Asp 1160	Thr	Thr	Ala	Ala	Gln 1165		Glu	Leu	Arg	Thr 1170		Arg	Glu
Gln	Glu 1175	Val	Ala	Glu		Lys 1180		Ala	Leu	Glu	Glu 1185	Glu	Thr	Lys
Asn	Ніs 1190	Glu	Ala	Gln	Ile	Gln 1195	Asp	Met	Arg	Gln	Arg 1200	His	Ala	Thr
Ala	Leu 1205	Glu	Glu	Leu		Glu 1210		Leu	Glu	Gln	Ala 1215		Arg	Phe
Lys	Ala 1220	Asn	Leu	Glu		Asn 1225		Gln	Gly		Glu 1230		Asp	Asn
Lys	Glu 1235	Leu	Ala	Cys	Glu	Val 1240		Val	Leu	Gln	Gln 1245		Lys	Ala
Glu	Ser 1250	Glu	His	Lys	Arg	Lys 1255	Lys	Leu	Asp	Ala	Gln 1260	Val	Gln	Glu
Leu	His 1265	Ala	Lys	Val	Ser	Glu 1270		Asp	Arg	Leu	Arg 1275	Val	Glu	Leu
Ala	Glu 1280	Lys	Ala	Ser		Leu 1285		Asn	Glu	Leu	Asp 1290		Val	Ser
	Leu 1295		Glu	Glu		Glu 1300		Lys	Gly	Ile	Lys 1305	Phe	Ala	Lys
Asp	Ala 1310	Ala	Ser	Leu	Glu	Ser 1315	Gln	Leu	Gln	Asp	Thr 1320		Glu	Leu
Leu	Gln 1325		Glu	Thr		Gln 1330		Leu	Asn	Leu	Ser 1335		Arg	Ile
Arg	Gln 1340		Glu	Glu		Lys 1345	Asn	Ser	Leu	Gln	Glu 1350	Gln	Gln	Glu
											Gln 1365		Leu	Ala
Leu	Gln 1370	Ser	Gln	Leu	Ala	Asp 1375	Thr	Lys	Lys	Lys	Val 1380	Asp	Asp	Asp
Leu	Gly 1385	Thr	Ile	Glu	Ser	Leu 1390	Glu	Glu	Ala	Lys	Lys 1395	Lys	Leu	Leu
Lys	Asp 1400	Ala	Glu	Ala	Leu	Ser 1405	Gln	Arg	Leu	Glu	Glu 1410	Lys	Ala	Leu
Ala	Tyr 1415	Asp	Lys	Leu	Glu	Lys 1420	Thr	Lys	Asn	Arg	Leu 1425	Gln	Gln	Glu

Leu Asp Asp Leu Thr Val Asp Leu Asp His Gln Arg Gln Val Ala 1430

Ser	Asn 1445	Leu	Glu	Lys	Lys	Gln 1450		Lys	Phe		Gln 1455	Leu	Leu	Ala
Glu	Glu 1460	Lys	Ser	Ile		Ala 1465		Tyr		Glu	Glu 1470	Arg	Asp	Arg
Ala	Glu 1475	Ala	Glu	Ala	Arg	Glu 1480		Glu	Thr		Ala 1485	Leu	Ser	Leu
Ala	Arg 1490	Ala	Leu	Glu	Glu	Ala 1495	Leu	Glu	Ala	Lys	Glu 1500	Glu	Phe	Glu
Arg	Gln 1505	Asn	Lys	Gln		Arg 1510		Asp	Met	Glu	Asp 1515	Leu	Met	Ser
Ser	Lys 1520	Asp	Asp	Val	Gly	Lys 1525	Asn	Val	His	Glu	Leu 1530	Glu	Lys	Ser
Lys	Arg 1535	Ala	Leu	Glu		Gln 1540		Glu	Glu	Met	Arg 1545		Gln	Leu
Glu	Glu 1550		Glu	Asp		Leu 1555		Ala	Thr	Glu	Asp 1560		Lys	Leu
Arg	Leu 1565	Glu	Val	Asn	Met	Gln 1570	Ala	Met	Lys	Ala	Gln 1575	Phe	Glu	Arg
Asp	Leu 1580	Gln	Thr	Arg		Glu 1585		Asn	Glu	Glu	Lys 1590	Lys	Arg	Leu
Leu	Ile 1595		Gln	Val	Arg	Glu 1600		Glu	Al'a	Glu	Leu 1605		Asp	Glu
Arg	Lys 1610	Gln	Arg	Ala	Leu	Ala 1615	Val	Ala	Ser	Lys	Lys 1620	Lys	Met	Glu
Ile	Asp 1625		Lys	Asp		Glu 1630		Gln	Ile	Glu	Ala 1635		Asn	Lys
Ala	Arg 1640	Asp	Glu	Val	Ile	Lys 1645	Gln	Leu	Arg	Lys	Leu 1650	Gln	Ala	Gln
Met	Lys 1655	Asp	туг	Gln	Arg	Glu 1660	Leu	Glu	Glu	Ala	Arg 1665	Ala	Ser	Arg
Asp	Glu 1670	Ile	Phe	Ala	Gln	Ser 1675	Lys	Glu	Ser	Glu	Lys 1680		Leu	Lys
Ser	Leu 1685	Glu	Ala	Glu	Ile	Leu 1690	Gln	Leu	Gln	Glu	Glu 1695		Ala	Ser
Ser	Glu 1700	Arg	Ala	Arg	Arg	His 1705	Ala	Glu	Gln	Glu	Arg 1710		Glu	Leu
Ala	Asp 1715	Glu	Ile	Thr	Asn	Ser 1720		Ser	Gly	Lys	Ser 1725	Ala	Leu	Leu
Asp	Glu 1730	Lys	Arg	Arg	Leu	Glu 1735		Arg	Ile	Ala	Gln 1740		Glu	Glu

Glu Leu Glu Glu Glu Gln Ser Asn Met Glu Leu Leu Asn Asp Arg 1745 1750 1755

Phe Arg Lys Thr Thr Leu Gln Val Asp Thr Leu Asn Ala Glu Leu 1760 1765 1770

Ala Ala Glu Arg Ser Ala Ala Gln Lys Ser Asp Asn Ala Arg Gln 1775 1780 1785

Gln Leu Glu Arg Gln Asn Lys Glu Leu Lys Ala Lys Leu Gln Glu 1790 1795 1800

Leu Glu Gly Ala Val Lys Ser Lys Phe Lys Ala Thr Ile Ser Ala 1805 1810 1815

Leu Glu Ala Lys Ile Gly Gln Leu Glu Glu Gln Leu Glu Glu Glu Gln Glu 1820 1830

Ala Lys Glu Arg Ala Ala Ala Asn Lys Leu Val Arg Arg Thr Glu 1835 1840 1845

Lys Lys Leu Lys Glu Ile Phe Met Gln Val Glu Asp Glu Arg Arg 1850 1860

His Ala Asp Gln Tyr Lys Glu Gln Met Glu Lys Ala Asn Ala Arg 1865 1870 1875

Met Lys Gln Leu Lys Arg Gln Leu Glu Glu Ala Glu Glu Glu Ala 1880 1885 1890

Thr Arg Ala Asn Ala Ser Arg Arg Lys Leu Gln Arg Glu Leu Asp 1895 1900 1905

Asp Ala Thr Glu Ala Asn Glu Gly Leu Ser Arg Glu Val Ser Thr 1910 1915 1920

Leu Lys Asn Arg Leu Arg Arg Gly Gly Pro Ile Ser Phe Ser Ser 1925 1930 1935

Ser Arg Ser Gly Arg Arg Gln Leu His Leu Glu Gly Ala Ser Leu 1940 1950 1950

Glu Leu Ser Asp Asp Asp Thr Glu Ser Lys Thr Ser Asp Val Asn 1955 1960 1965

Glu Thr Gln Pro Pro Gln Ser Glu

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<212> PRT

<213> Homo sapiens

<400> 158

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Phe Gln Ala Phe Met Lys Asn Gly Lys Leu Phe Cys Pro Gln Asp Lys 35 40 45

Lys Phe Phe Gln Ser Leu Asp Gly Ile Met Phe Ile Asn Lys Cys Ala 50 60

Thr Cys Lys Met Ile Leu Glu Lys Glu Ala Lys Ser Gln Lys Arg Ala 65 70 75 80

Arg His Leu Ala Arg Ala Pro Lys Ala Thr Ala Pro Thr Glu Leu Asn 85 90 95

Asp Tyr Tyr Glu Ala Val Cys Gly Thr Asp Gly Lys Thr Tyr Asp Asn  $115 \hspace{1.5cm} 120 \hspace{1.5cm} 125 \hspace{1.5cm}$ 

Arg Cys Ala Leu Cys Ala Glu Asn Ala Lys Thr Gly Ser Gln Ile Gly 130 135 140

Val Lys Ser Glu Gly Glu Cys Lys Ser Ser Asn Pro Glu Gln Asp Val 145 150 155 160

Cys Ser Ala Phe Arg Pro Phe Val Arg Asp Gly Arg Leu Gly Cys Thr 165 170 175

Arg Glu Asn Asp Pro Val Leu Gly Pro Asp Gly Lys Thr His Gly Asn 180 185 190

Lys Cys Ala Met Cys Ala Glu Leu Phe Leu Lys Glu Ala Glu Asn Ala 195 200 205

Lys Arg Glu Gly Glu Thr Arg Ile Arg Arg Asn Ala Glu Lys Asp Phe 210 225 220

Cys Lys Glu Tyr Glu Lys Gln Val Arg Asn Gly Arg Leu Phe Cys Thr 225 230 235 Phe Cys Thr 240

Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly Arg Met His Gly Asn 245 250 250 255

Lys Cys Ala Leu Cys Ala Glu Ile Phe Lys Arg Arg Phe Ser Glu Glu 260 265 270

As Ser Lys Thr Asp Gln Asn Leu Gly Lys Ala Glu Glu Lys Thr Lys 275 280 285

Val Lys Arg Glu Ile Val Lys Leu Cys Ser Gln Tyr Gln Asn Gln Ala 290 295 300

Lys Asn Gly Ile Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Arg Gly 305 310 315 320

Pro Asp Gly Lys Met His Gly Asn Leu Cys Ser Met Cys Gln Val Tyr 325 330 335

Phe Gln Ala Glu Asn Glu Glu Lys Lys Lys Ala Glu Ala Arg Ala Arg 340 345 350

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Asn Lys Arg Glu Ser Gly Lys Ala Thr Ser Tyr Ala Glu Leu Cys Asn 355 360 365

Glu Tyr Arg Lys Leu Val Arg Asn Gly Lys Leu Ala Cys Thr Arg Glu 370 375 380

Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys Val His Gly Asn Thr Cys 385 390 395 400

Ser Met Cys Glu Val Phe Phe Gln Ala Glu Glu Glu Glu Lys Lys Lys 405 410 415

Lys Glu Gly Glu Ser Arg Asn Lys Arg Gln Ser Lys Ser Thr Ala Ser 420 425 430

Phe Glu Glu Leu Cys Ser Glu Tyr Arg Lys Ser Arg Lys Asn Gly Arg 435 440 445

Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys 450 455 460

Glu Arg Ala Arg Ala Lys Ala Lys Arg Glu Ala Ala Lys Glu Ile Cys 485 490 495

Ser Glu Phe Arg Asp Gln Val Arg Asn Gly Thr Leu Ile Cys Thr Arg  $500 \hspace{1.5cm} 505 \hspace{1.5cm} 510$ 

Glu His Asn Pro Val Arg Gly Pro Asp Gly Lys Met His Gly Asn Lys 515 520 525

Cys Ala Met Cys Ala Ser Val Phe Lys Leu Glu Glu Glu Glu Lys Lys 530 535 540

Asn Asp Lys Glu Glu Lys Gly Lys Val Glu Ala Glu Lys Val Lys Arg 545 550 560

Glu Ala Val Gln Glu Leu Cys Ser Glu Tyr Arg His Tyr Val Arg Asn 565 570 575

Gly Arg Leu Pro Cys Thr Arg Glu Asn Asp Pro Ile Glu Gly Leu Asp 580 585 590

Gly Lys Ile His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln 595 600 605

Gln Glu Ala Lys Glu Lys Glu Arg Ala Glu Pro Arg Ala Lys Val Lys 610 615 620

Arg Glu Ala Glu Lys Glu Thr Cys Asp Glu Phe Arg Arg Leu Leu Gln 625 630 635

Asn Gly Lys Leu Phe Cys Thr Arg Glu Asn Asp Pro Val Arg Gly Pro 645 650 655

Asp Gly Lys Thr His Gly Asn Lys Cys Ala Met Cys Lys Ala Val Phe Page 251 660 665 670

Gln Lys Glu Asn Glu Glu Arg Lys Arg Lys Glu Glu Glu Asp Gln Arg 675

Asn Ala Ala Gly His Gly Ser Ser Gly Gly Gly Gly Gly Asn Thr Gln 690

Asp Glu Cys Ala Glu Tyr Gln Glu Gln Met Lys Asn Gly Arg Leu Ser 720

Cys Thr Arg Glu Ser Asp Pro Val Arg Asp Ala Asp Gly Lys Ser Tyr 735

Arg Lys Asn Glu Tyr Ser Arg Ser Arg Ser Asn Gly Thr Gly Ser Glu 755 760 765

Ser Gly Lys Asp Thr Cys Asp Glu Phe Arg Ser Gln Met Lys Asn Gly  $770 \hspace{1cm} 775 \hspace{1cm} 780$ 

Lys Leu Ile Cys Thr Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly 785  $\phantom{\bigg|}790\phantom{\bigg|}790\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}790\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795\phantom{\bigg|}795$ 

Gly Glu Arg Ser Asn Thr Gly Glu Arg Ser Asn Asp Lys Glu Asp Leu 835 840 845

Cys Arg Glu Phe Arg Ser Met Gln Arg Asn Gly Lys Leu Ile Cys Thr 850 860

Arg Glu Asn Asn Pro Val Arg Gly Pro Tyr Gly Lys Met His Ile Asn 865 870 870 875

Lys Cys Ala Met Cys Gln Ser Ile Phe Asp Arg Glu Ala Asn Glu Arg 885 890 895

Lys Lys Lys Asp Glu Glu Lys Ser Ser Ser Lys Pro Ser Asn Asn Ala 900 905 910

Lys Asp Glu Cys Ser Glu Phe Arg Asn Tyr Ile Arg Asn Asn Glu Leu 915 920 925

Ile Cys Pro Arg Glu Asn Asp Pro Val His Gly Ala Asp Gly Lys Phe 930 940

Tyr Thr Asn Lys Cys Tyr Met Cys Arg Ala Val Phe Leu Thr Glu Ala 945 950 955 960

Leu Glu Arg Ala Lys Leu Gln Glu Lys Pro Ser His Val Arg Ala Ser 965 970 970 975

Gln Glu Glu Asp Ser Pro Asp Ser Phe Ser Ser Leu Asp Ser Glu Met 980 985 990

Cys Lys Asp Tyr Arg Val Leu Pro Arg Ile Gly Tyr Leu Cys Pro Lys 995 1000 1005

Asp Leu Lys Pro Val Cys Gly Asp Asp Gly Gln Thr Tyr Asn Asn 1010 1020

Pro Cys Met Leu Cys His Glu  $\mbox{ Asn Leu Ile Arg Gln }\mbox{ Thr Asn Thr} \mbox{ 1025} \mbox{ 1030}$ 

His Ile Arg Ser Thr Gly Lys Cys Glu Glu Ser Ser Thr Pro Gly 1040 1045

Thr Thr Ala Ala Ser Met Pro Pro Ser Asp Glu 1055  $\,$  1060

<210> 159

<211> 125 <212> PRT

<213> Homo sapiens

<400> 159

Met His Lys Glu Glu His Glu Val Ala Val Leu Gly Ala Pro Pro Ser

Thr Ile Leu Pro Arg Ser Thr Val Ile Asn Ile His Ser Glu Thr Ser 20 25 30

Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr Leu Phe Leu Asn  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Trp Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser Val Lys Ser Arg 50 60

Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln Ala Tyr Ala Ser 65 70 75 80

Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu Gly Ile Leu Met 85 90 95

Thr Ile Gly Phe Ile Leu Leu Leu Val Phe Gly Ser Val Thr Val Tyr  $100 \hspace{1cm} 105 \hspace{1cm} 105 \hspace{1cm} 110 \hspace{1cm}$ 

His Ile Met Leu Gln Ile Ile Gln Glu Lys Arg Gly Tyr 115 120 125

<213> Homo sapiens

<400> 160

Met Met Asp Leu Arg Asn Thr Pro Ala Lys Ser Leu Asp Lys Phe Ile 1 10 15

Glu Asp Tyr Leu Leu Pro Asp Thr Cys Phe Arg Met Gln Ile Asp His  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Ala Ile Asp Ile Ile Cys Gly Phe Leu Lys Glu Arg Cys Phe Arg Gly Page 253

ar.	40	45
35	40	7.5

Phe Leu Ser Pro Leu Thr Thr Phe Gln Asp Gln Leu Asn Arg Arg Gly 85 90 95

Glu Phe Ile Gln Glu Ile Arg Arg Gln Leu Glu Ala Cys Gln Arg Glu 100 105 110

Arg Ala Leu Ser Val Lys Phe Glu Val Gln Ala Pro Arg Trp Gly Asn  $115 \hspace{1.5cm} 120 \hspace{1.5cm} 125$ 

Pro Arg Ala Leu Ser Phe Val Leu Ser Ser Leu Gln Leu Gly Glu Gly 130 135 140

Val Glu Phe Asp Val Leu Pro Ala Phe Asp Ala Leu Gly Gln Leu Thr 145 150 150 160

Gly Ser Tyr Lys Pro Asn Pro Gln Ile Tyr Val Lys Leu Ile Glu Glu 165 170 175

Cys Thr Asp Leu Gln Lys Glu Glu Glu Phe Ser Thr Cys Phe Thr Glu 180 185 190

Leu Gln Arg Asp Phe Leu Lys Gln Arg Pro Thr Lys Leu Lys Ser Leu 195 200 205

Ile Arg Leu Val Lys His Trp Tyr Gln Asn Cys Lys Lys Lys Leu Gly 210 215 220

Lys Leu Pro Pro Gln Tyr Ala Leu Glu Leu Leu Thr Val Tyr Ala Trp 225 230 235 240

Glu Arg Gly Ser Met Lys Thr His Phe Asn Thr Ala Gln Gly Phe Arg 245 250 255

Thr Val Leu Glu Leu Val Ile Asn Tyr Gln Gln Leu Cys Ile Tyr Trp  $260 \hspace{1cm} 265 \hspace{1cm} 265 \hspace{1cm} 270 \hspace{1cm}$ 

Thr Lys Tyr Tyr Asp Phe Lys Asn Pro Ile Ile Glu Lys Tyr Leu Arg 275 280 285

Arg Gln Leu Thr Lys Pro Arg Pro Val Ile Leu Asp Pro Ala Asp Pro 290 295 300

Thr Gly Asn Leu Gly Gly Gly Asp Pro Lys Gly Trp Arg Gln Leu Ala 305 310 315 320

Gln Glu Ala Glu Ala Trp Leu Asn Tyr Pro Cys Phe Lys Asn Trp Asp 325 330 335

Gly Ser Pro Val Ser Ser Trp Ile Leu Leu Ala Glu Ser Asn Ser Thr 340 345 350

Asp Asp Glu Thr Asp Asp Pro Arg Thr Tyr Gln Lys Tyr Gly Tyr Ile  $355 \hspace{1.5cm} 360 \hspace{1.5cm} 365$ 

Gly Thr His Glu Tyr Pro His Phe Ser His Arg Pro Ser Thr Leu Gln 370 375 380

Ala Ala Ser Thr Pro Gln Ala Glu Glu Asp Trp Thr Cys Thr Ile Leu 385 390 395 400

<210> 161

<211> 370

<212> PRT

<213> Homo sapiens

<400> 161

Met Glu Asn Gln Val Leu Thr Pro His Val Tyr Trp Ala Gln Arg His 1 5 10 15

Arg Glu Leu Tyr Leu Arg Val Glu Leu Ser Asp Val Gln Asn Pro Ala  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30 \hspace{1.5cm}$ 

Ile Ser Ile Thr Glu Asn Val Leu His Phe Lys Ala Gln Gly His Gly 35 40 45

Ala Lys Gly Asp Asn Val Tyr Glu Phe His Leu Glu Phe Leu Asp Leu 50 60

Val Lys Pro Glu Pro Val Tyr Lys Leu Thr Gln Arg Gln Val Asn Ile 65 70 75 80

Thr Val Gln Lys Lys Val Ser Gln Trp Trp Glu Arg Leu Thr Lys Gln 85 90 90 95

Glu Lys Arg Pro Leu Phe Leu Ala Pro Asp Phe Asp Arg Trp Leu Asp  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

Glu Ser Asp Ala Glu Met Glu Leu Arg Ala Lys Glu Glu Glu Arg Leu 115 120 125

Asn Lys Leu Arg Leu Glu Ser Glu Gly Ser Pro Glu Thr Leu Thr Asn 130  $$135\$ 

Leu Arg Lys Gly Tyr Leu Phe Met Tyr Asn Leu Val Gln Phe Leu Gly 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ 

Phe Ser Trp Ile Phe Val Asn Leu Thr Val Arg Phe Cys Ile Leu Gly 165 170 175

Lys Glu Ser Phe Tyr Asp Thr Phe His Thr Val Ala Asp Met Met Tyr 180 195 190

Phe Cys Gln Met Leu Ala Val Val Glu Thr Ile Asn Ala Ala Ile Gly 195 200 205

Val Thr Thr Ser Pro Val Leu Pro Ser Leu Ile Gln Leu Leu Gly Arg 210 215 220

Asn Phe Ile Leu Phe Ile Ile Phe Gly Thr Met Glu Glu Met Gln Asn 225 230 235 240

Lys Ala Val Val Phe Phe Val Phe Tyr Leu Trp Ser Ala Ile Glu Ile 245 250 255

Phe Arg Tyr Ser Phe Tyr Met Leu Thr Cys Ile Asp Met Asp Trp Lys 260 265 270

Val Leu Thr Trp Leu Arg Tyr Thr Leu Trp Ile Pro Leu Tyr Pro Leu 275 280 285

Gly Cys Leu Ala Glu Ala Val Ser Val Ile Gln Ser Ile Pro Ile Phe 290 295 300

Asn Glu Thr Gly Arg Phe Ser Phe Thr Leu Pro Tyr Pro Val Lys Ile 305 310 315 320

Lys Val Arg Phe Ser Phe Phe Leu Gln Ile Tyr Leu Ile Met Ile Phe 325 330 335

Leu Gly Leu Tyr Ile Asn Phe Arg His Leu Tyr Lys Gln Arg Arg Leu 340 345 350

Gly Gly 370

<210> 162

<211> 372

<212> PRT

<213> Homo sapiens

<400> 162

Met Leu Asp Gly Leu Gly Val Val Ala Ile Ser Ile Phe Gly Ile Gln 1  $\phantom{\Big|}$  10  $\phantom{\Big|}$  15

Leu Lys Thr Glu Gly Ser Leu Arg Thr Ala Val Pro Gly Ile Pro Thr  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Gln Ser Ala Phe Asn Lys Cys Leu Gln Arg Tyr Ile Gly Ala Leu Gly 35 40 45

Ala Arg Val Ile Cys Asp Asn Ile Pro Gly Leu Val Ser Arg Gln Arg 50 60

Gln Leu Cys Gln Arg Tyr Pro Asp Ile Met Arg Ser Val Gly Glu Gly 65 70 75 80

Ala Arg Glu Trp Ile Arg Glu Cys Gln His Gln Phe Arg His His Arg 85 90 95

Trp Asn Cys Thr Thr Leu Asp Arg Asp His Thr Val Phe Gly Arg Val 100 105 110

Met Leu Arg Ser Ser Arg Glu Ala Ala Phe Val Tyr Ala Ile Ser Ser 115 120 125

Ala Gly Val Ile His Ala Ile Thr Arg Ala Cys Ser Gln Gly Glu Leu 130 135 140

Ser Val Cys Ser Cys Asp Pro Tyr Thr Arg Gly Arg His His Asp Gln 145 150 155 160

Arg Gly Thr Phe Asp Trp Gly Gly Cys Ser Asp Asn Ile His Tyr Gly 165 170 175

Val Arg Phe Ala Lys Ala Phe Val Asp Ala Lys Glu Lys Arg Leu Lys 180 185 190

Asp Ala Arg Ala Leu Met Asn Leu His Asn Asn Arg Cys Gly Arg Thr 195 200 205

Ala Val Arg Arg Phe Val Lys Leu Glu Cys Lys Cys His Gly Val Ser 210 220

Gly Ser Cys Thr Leu Arg Thr Cys Trp Arg Ala Leu Ser Asp Phe Arg 225 230 240

Arg Thr Gly Asp Tyr Leu Arg Arg Arg Tyr Asp Gly Ala Val Gln Val 245 250 250

Met Ala Thr Gln Asp Gly Ala Asn Phe Thr Ala Ala Arg Gln Gly Tyr 260 265 270

Arg Arg Ala Thr Arg Ser Asp Leu Val Tyr Phe Asp Asn Ser Pro Asp 275 280 285

Tyr Cys Val Leu Asp Lys Ala Ala Gly Ser Leu Gly Thr Ala Gly Arg 290 295 300

Val Cys Ser Lys Thr Ser Lys Gly Thr Asp Gly Cys Glu Ile Met Cys 305  $\phantom{\bigg|}310\phantom{\bigg|}315\phantom{\bigg|}315\phantom{\bigg|}$ 

Cys Gly Arg Gly Tyr Asp Thr Thr Arg Val Thr Arg Val Thr Gln Cys 325 330 335

Glu Cys Lys Phe His Trp Cys Cys Ala Val Arg Cys Lys Glu Cys Arg 340 345 350

As nThr Val Asp Val His Thr Cys Lys Ala Pro Lys Lys Ala Glu Trp 355 360 365

Leu Asp Gln Thr 370

(210> 163

<211> 249

<211> 243 <212> PRT

<213> Homo sapiens

<400> 163

Met Lys Leu Asn Ile Ser Phe Pro Ala Thr Gly Cys Gln Lys Leu Ile 1 10 15

Glu Val Asp Asp Glu Arg Thr Leu Arg Thr Phe Tyr Glu Lys Arg Met 20 25 30

Ala Thr Glu Val Ala Ala Asp Ala Leu Gly Glu Glu Trp Lys Gly Tyr  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Val Val Arg Ile Ser Gly Gly Asn Asp Lys Gln Gly Phe Pro Met Lys 50 60

Gln Gly Val Leu Thr His Gly Arg Val Arg Leu Leu Ser Lys Gly 65 70 75 80

His Ser Cys Tyr Arg Pro Arg Arg Thr Gly Glu Arg Lys Arg Lys Ser 85 90 95

Val Arg Gly Cys Ile Val Asp Ala Asn Leu Ser Val Leu Asn Leu Val 100 105 110

Ile Val Lys Lys Gly Glu Lys Asp Ile Pro Gly Leu Thr Asp Thr Thr  $115 \hspace{1.5cm} 120 \hspace{1.5cm} 125$ 

Val Pro Arg Arg Leu Gly Pro Lys Arg Ala Ser Arg Ile Arg Lys Arg 130 135 140

Phe Asn Leu Ser Lys Glu Asp Asp Val Arg Gln Tyr Val Val Arg Lys 145 150 150 160

Pro Leu Asn Lys Glu Gly Lys Lys Pro Arg Thr Lys Ala Pro Lys Ile  $165 \\ 170 \\ 170 \\ 175$ 

Gln Arg Leu Val Thr Pro Arg Val Leu Gln His Lys Arg Arg Arg Ile 180 185 190

Ala Leu Lys Gln Gln Arg Thr Lys Lys Asn Lys Glu Glu Ala Ala Glu 195 200 205

Tyr Ala Lys Leu Leu Ala Lys Arg Met Lys Glu Ala Lys Glu Lys Arg 210 215 220

Gln Glu Gln Ile Ala Lys Arg Arg Arg Leu Ser Ser Leu Arg Ala Ser 225 230 230 235

Thr Ser Lys Ser Glu Ser Ser Gln Lys 245

<210> 164

<211> 469

<212> PRT <213> Homo sapiens

<400> 164

Met His Ser Phe Pro Pro Leu Leu Leu Leu Phe Trp Gly Val Val 1 10 15

Ser His Ser Phe Pro Ala Thr Leu Glu Thr Gln Glu Gln Asp Val Asp  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Leu Val Gln Lys Tyr Leu Glu Lys Tyr Tyr Asn Leu Lys Asn Asp Gly 35 40 45

Arg Gln Val Glu Lys Arg Arg Asn Ser Gly Pro Val Val Glu Lys Leu  $50 \hspace{1cm} 55 \hspace{1cm} 60$ 

Lys Gln Met Gln Glu Phe Phe Gly Leu Lys Val Thr Gly Lys Pro Asp 65 70 75 80

Ala Glu Thr Leu Lys Val Met Lys Gln Pro Arg Cys Gly Val Pro Asp  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Val Ala Gln Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr 100 105 110

His Leu Thr Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala 115 120 125

Asp Val Asp His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val 130 135 140

Thr Pro Leu Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}160\phantom{\bigg|}$ 

Ile Ser Phe Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly 165 170 175

Pro Gly Gly Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly 180  $$185\$ 

Gly Asp Ala His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg 195 200 205

Glu Tyr Asn Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu 210 215 220

Gly Leu Ser His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr 225 230 235 240

Thr Phe Ser Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255$ 

Gln Ala Ile Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro 260 265 270

Gln Thr Pro Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr 275 280 285

Thr Ile Arg Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg 290 295 300

Thr Asn Pro Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe 305 310 315 320

Trp Pro Gln Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp  $325 \hspace{1cm} 330 \hspace{1cm} 335$ 

Arg Asp Glu Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln 340 345 350

Gly Gln Asn Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe 355 360 365

Gly Phe Pro Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu 370 380

Asn Thr Gly Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr 385 390 395 400

Asp Glu Tyr Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala 405 410 415

His Asp Phe Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys 420 425 430

Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp  $435 \hspace{1.5cm} 440 \hspace{1.5cm} 445$ 

Pro Lys Thr Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe 450 455 460

Asn Cys Arg Lys Asn

<212> PRT

<213> Homo sapiens

<400> 165

Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp 20 25 30

Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys 35 40 45

Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu 50 60

Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Ala Lys Lys Arg 65 70 75 80

Lys Lys Lys Ser Tyr Thr Thr Pro Lys Lys Asn Lys His Lys Arg Lys 85 90 95

Lys Val Lys Leu Ala Val Leu Lys Tyr Tyr Lys Val Asp Glu Asn Gly  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

Lys Ile Ser Arg Leu Arg Arg Glu Cys Pro Ser Asp Glu Cys Gly Ala 115 120 125

Gly Val Phe Met Ala Ser His Phe Asp Arg His Tyr Cys Gly Lys Cys 130 135 140

Cys Leu Thr Tyr Cys Phe Asn Lys Pro Glu Asp Lys 145  $\phantom{\bigg|}150\phantom{\bigg|}$  155

<210> 166 <211> 783 <212> PRT

<213> Homo sapiens

<400> 166

Met Ala Lys Tyr Asn Thr Gly Gly Asn Pro Thr Glu Asp Val Ser Val 1 10 15

As Ser Arg Pro Phe Arg Val Thr Gly Pro As Ser Ser Ser Gly Ile  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$ 

Gln Ala Arg Lys Asn Leu Phe Asn Asn Gln Gly Asn Ala Ser Pro Pro 35 40 45

Ala Gly Pro Ser Asn Val Pro Lys Phe Gly Ser Pro Lys Pro Pro Val 50 60

Ala Val Lys Pro Ser Ser Glu Glu Lys Pro Asp Lys Glu Pro Lys Pro 65 70 75 80

Pro Phe Leu Lys Pro Thr Gly Ala Gly Gln Arg Phe Gly Thr Pro Ala 85 90 95

Ser Leu Thr Thr Arg Asp Pro Glu Ala Lys Val Gly Phe Leu Lys Pro 100 105 110

Val Gly Pro Lys Pro Ile Asn Leu Pro Lys Glu Asp Ser Lys Pro Thr 115 120 125

Phe Pro Trp Pro Pro Gly Asn Lys Pro Ser Leu His Ser Val Asn Gln 130 135 140

Asp His Asp Leu Lys Pro Leu Gly Pro Lys Ser Gly Pro Thr Pro Pro 145 150 160

Thr Ser Glu Asn Glu Gln Lys Gln Ala Phe Pro Lys Leu Thr Gly Val 165 170 175

Lys Gly Lys Phe Met Ser Ala Ser Gln Asp Leu Glu Pro Lys Pro Leu 180 185 190

Phe Pro Lys Pro Ala Phe Gly Gln Lys Pro Pro Leu Ser Thr Glu Asn 195 200 205

Ser His Glu Asp Glu Ser Pro Met Lys Asn Val Ser Ser Ser Lys Gly 210 215 220

Ser Pro Ala Pro Leu Gly Val Arg Ser Lys Ser Gly Pro Leu Lys Pro 225 230 230 240

Ala Arg Glu Asp Ser Glu Asn Lys Asp His Ala Gly Glu Ile Ser Ser 245 250 255

Leu Pro Phe Pro Gly Val Val Leu Lys Pro Ala Ala Ser Arg Ġly Gly 260 265 270

Leu Gly Leu Ser Lys Asn Gly Glu Glu Lys Lys Glu Asp Arg Lys Ile  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285$ 

Asp Ala Ala Lys Asn Thr Phe Gln Ser Lys Ile Asn Gln Glu Glu Leu 290 295 300

Ala Ser Gly Thr Pro Pro Ala Arg Phe Pro Lys Ala Pro Ser Lys Leu 305 310 315 320

Thr Val Gly Gly Pro Trp Gly Gln Ser Gln Glu Lys Glu Lys Gly Asp 325 330 335

Lys Asn Ser Ala Thr Pro Lys Gln Lys Pro Leu Pro Pro Leu Phe Thr 340 345 350

Leu Gly Pro Pro Pro Pro Lys Pro Asn Arg Pro Pro Asn Val Asp Leu 355 360 365

Thr Lys Phe His Lys Thr Ser Ser Gly Asn Ser Thr Ser Lys Gly Gln 370 375 380

Thr Ser Tyr Ser Thr Thr Ser Leu Pro Pro Pro Pro Pro Ser His Pro 385 390 395 400

Ala Ser Gln Pro Pro Leu Pro Ala Ser His Pro Ser Gln Pro Pro Val405 410 415

Pro Ser Leu Pro Pro Arg Asn Ile Lys Pro Pro Phe Asp Leu Lys Ser 420 425 430

Pro Val Asn Glu Asp Asn Gln Asp Gly Val Thr His Ser Asp Gly Ala 435 440 445

Gly Asn Leu Asp Glu Glu Gln Asp Ser Glu Gly Glu Thr Tyr Glu Asp 450 460

Ile Glu Ala Ser Lys Glu Arg Glu Lys Lys Arg Glu Lys Glu Glu Lys 465 470 480

Lys Arg Leu Glu Leu Glu Lys Lys Glu Gln Lys Glu Lys Glu Lys Lys 485 490 490 495

Glu Gln Glu Ile Lys Lys Phe Lys Leu Thr Gly Pro Ile Gln Val $500 \ \ 505 \ \ \ 510$ 

Ile His Leu Ala Lys Ala Cys Cys Asp Val Lys Gly Gly Lys Asn Glu 515 520 525

Leu Ser Phe Lys Gln Gly Glu Gln Ile Glu Ile Ile Arg Ile Thr Asp 530 535 540

Asn Pro Glu Gly Lys Trp Leu Gly Arg Thr Ala Arg Gly Ser Tyr Gly 545 550 560

Tyr Ile Lys Thr Thr Ala Val Glu Ile Asp Tyr Asp Ser Leu Lys Leu 565 570 575

Lys Lys Asp Ser Leu Gly Ala Pro Ser Arg Pro Ile Glu Asp Asp Gln  $580 \,$   $585 \,$  590

Glu Val Tyr Asp Asp Val Ala Glu Gln Asp Asp Ile Ser Ser His Ser 595 600 605

Gln Ser Gly Ser Gly Gly Ile Phe Pro Pro Pro Pro Asp Asp Asp Ile 610 615 620

Tyr Asp Gly Ile Glu Glu Glu Asp Ala Asp Asp Gly Phe Pro Ala Pro 625 630 635 640

Pro Lys Gln Leu Asp Met Gly Asp Glu Val Tyr Asp Asp Val Asp Thr  $645 \hspace{1cm} 650 \hspace{1cm} 655$ 

Ser Asp Phe Pro Val Ser Ser Ala Glu Met Ser Gln Gly Thr Asn Phe  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670$ 

Gly Lys Ala Lys Thr Glu Glu Lys Asp Leu Lys Lys Leu Lys Lys Gln 675 680 685

Glu Lys Glu Glu Lys Asp Phe Arg Lys Lys Phe Lys Tyr Asp Gly Glu 690 695 700

Ile Arg Val Leu Tyr Ser Thr Lys Val Thr Thr Ser Ile Thr Ser Lys 705 710 715 720

Lys Trp Gly Thr Arg Asp Leu Gln Val Lys Pro Gly Glu Ser Leu Glu 725 730 735

Val \lambda Ile Gln Thr Thr Asp Asp Thr Lys Val Leu Cys Arg Asn Glu Glu 740 745 750

Gly Lys Tyr Gly Tyr Val Leu Arg Ser Tyr Leu Ala Asp Asn Asp Gly  $755 \hspace{1cm} 760 \hspace{1cm} 765$ 

Glu Ile Tyr Asp Asp Ile Ala Asp Gly Cys Ile Tyr Asp Asn Asp 770  $\phantom{000}$  775  $\phantom{000}$  780

<210> 167

<211> 117

<212> PRT <213> Homo sapiens

<400> 167

Met Ala Ala Ala Ala Ala Gly Ser Gly Thr Pro Arg Glu Glu Glu 1 10 15

Val Pro Ala Gly Glu Ala Ala Ala Ser Gln Pro Gln Ala Pro Thr Ser 20 25 30

Val Pro Gly Ala Arg Leu Ser Arg Leu Pro Leu Ala Arg Val Lys Ala 35 40 45

Leu Val Lys Ala Asp Pro Asp Val Thr Leu Ala Gly Gln Glu Ala Ile 50 60

Phe Ile Leu Ala Arg Ala Ala Glu Leu Phe Val Glu Thr Ile Ala Lys 65 70 75 80

Asp Ala Tyr Cys Cys Ala Gln Gln Gly Lys Arg Lys Thr Leu Gln Arg 85 90 95

Arg Asp Leu Asp Asn Ala Ile Glu Ala Val Asp Glu Phe Ala Phe Leu  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110$ 

Glu Gly Thr Leu Asp 115

<210> 168 <211> 243

<211> 243 <212> PRT

<213> Homo sapiens

<400> 168

Met Ala Val Gln Ile Ser Lys Arg Arg Lys Phe Val Ala Asp Gly Ile

Phe Lys Ala Glu Leu Asn Glu Phe Leu Thr Arg Glu Leu Ala Glu Asp 20 25 30

Gly Tyr Ser Gly Val Glu Val Arg Val Thr Pro Thr Arg Thr Glu Ile  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Ile Ile Leu Ala Thr Arg Thr Gln Asn Val Leu Gly Glu Lys Gly Arg 50 55 60

Arg Ile Arg Glu Leu Thr Ala Val Val Gln Lys Arg Phe Gly Phe Pro 65 70 75 80

Glu Gly Ser Val Glu Leu Tyr Ala Glu Lys Val Ala Thr Arg Gly Leu  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Cys Ala Ile Ala Gln Ala Glu Ser Leu Arg Tyr Lys Leu Leu Gly Gly 100 105 110

Leu Ala Val Arg Arg Ala Cys Tyr Gly Val Leu Arg Phe Ile Met Glu 115 120 125

Ser Gly Ala Lys Gly Cys Glu Val Val Val Ser Gly Lys Leu Arg Gly 130 135 140

Gln Arg Ala Lys Ser Met Lys Phe Val Asp Gly Leu Met Ile His Ser 145 150 155 160

Gly Asp Pro Val Asn Tyr Tyr Val Asp Thr Ala Val Arg His Val Leu 165 170 175

Leu Arg Gln Gly Val Leu Gly Ile Lys Val Lys Ile Met Leu Pro Trp

Asp Pro Thr Gly Lys Ile Gly Pro Lys Lys Pro Leu Pro Asp His Val

Ser Ile Val Glu Pro Lys Asp Glu Ile Leu Pro Thr Thr Pro Ile Ser 210 215 220

Glu Gln Lys Gly Gly Lys Pro Glu Pro Pro Ala Met Pro Gln Pro Val 225 230 235 240

Pro Thr Ala

<210> 169

<211> 136 <212> PRT

<213> Homo sapiens

<400> 169

Met Val Leu Leu Glu Ser Glu Gln Phe Leu Thr Glu Leu Thr Arg Leu 1  $\overset{\circ}{\phantom{}}$  10 15

Phe Gln Lys Cys Arg Thr Ser Gly Ser Val Tyr Ile Thr Leu Lys Lys 20 25 30

Tyr Asp Gly Arg Thr Lys Pro Ile Pro Lys Lys Gly Thr Val Glu Gly  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Phe Glu Pro Ala Asp Asn Lys Cys Leu Leu Arg Ala Thr Asp Gly Lys 50 60

Lys Lys Ile Ser Thr Val Val Ser Ser Lys Glu Val Asn Lys Phe Gln 65 70 75 80

Met Ala Tyr Ser Asn Leu Leu Arg Ala Asn Met Asp Gly Leu Lys Lys 85 90 95

Arg Asp Lys Lys Asn Lys Thr Lys Lys Thr Lys Ala Ala Ala Ala Ala 100 105 110

Ala Ala Ala Ala Pro Ala Ala Ala Ala Thr Ala Ala Thr Thr Ala Ala 115 120 125

Thr Thr Ala Ala Thr Ala Ala Gln 130 135

<210> 170

<211> 409

<212> PRT

<213> Homo sapiens

<400> 170

Glu Lys Gly Lys Asp Ala Phe Pro Val Ala Gly Gln Lys Leu Ile Tyr  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Ala Gly Lys Ile Leu Asn Asp Asp Thr Ala Leu Lys Glu Tyr Lys Ile 50 60

Asp Glu Lys Asn Phe Val Val Val Met Val Thr Lys Pro Lys Ala Val 65 70 75 80

Ser Thr Pro Ala Pro Ala Thr Thr Gln Gln Ser Ala Pro Ala Ser Thr 85 90 95

Thr Ala Val Thr Ser Ser Thr Thr Thr Thr Val Ala Gln Ala Pro Thr 100 \$105\$

Pro Val Pro Ala Leu Ala Pro Thr Ser Thr Pro Ala Ser Ile Thr Pro 115 120 125

Ala Ser Ala Thr Ala Ser Ser Glu Pro Ala Pro Ala Ser Ala Ala Lys 130 135 140

Gln Glu Lys Pro Ala Glu Lys Pro Ala Glu Thr Pro Val Ala Thr Ser 145 150 155 160

Pro Thr Ala Thr Asp Ser Thr Ser Gly Asp Ser Ser Arg Ser Asn Leu 165 170 175 Phe Glu Asp Ala Thr Ser Ala Leu Val Thr Gly Gln Ser Tyr Glu Asn 180  $$185\mathcharpoons$ 

Met Val Thr Glu Ile Met Ser Met Gly Tyr Glu Arg Glu Gln Val Ile 195 200 205

Ala Ala Leu Arg Ala Ser Phe Asn Asn Pro Asp Arg Ala Val Glu Tyr 210 215 220

Leu Leu Met Gly Ile Pro Gly Asp Arg Glu Ser Gln Ala Val Val Asp 225 230 235 240

Pro Pro Gln Ala Ala Ser Thr Gly Ala Pro Gln Ser Ser Ala Val Ala 245 250 255

Ala Ala Ala Ala Thr Thr Thr Ala Thr Thr Thr Thr Thr Ser Ser Gly  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$ 

Arg Gln Ile Ile Gln Gln Asn Pro Ser Leu Leu Pro Ala Leu Leu Gln 290 295 300

Gln Ile Gly Arg Glu Asn Pro Gln Leu Leu Gln Gln Ile Ser Gln His 305 310 315 320

Gln Glu His Phe Ile Gln Met Leu Asn Glu Pro Val Gln Glu Ala Gly 325 330 335

Gly Gln Gly Gly Gly Gly Gly Gly Ser Gly Gly Ile Ala Glu Ala 340 \$345\$

Gly Ser Gly His Met Asn Tyr Ile Gln Val Thr Pro Gln Glu Lys Glu 355 360 365

Ala Ile Glu Arg Leu Lys Ala Leu Gly Phe Pro Glu Gly Leu Val Ile 370 375 380

Gln Ala Tyr Phe Ala Cys Glu Lys Asn Glu Asn Leu Ala Ala Asn Phe 385 390 395 400

Leu Leu Gln Gln Asn Phe Asp Glu Asp 405

<210> 171 <211> 614

<212> PRT

<213> Homo sapiens

Met Ser Gly Ile Lys Lys Gln Lys Thr Glu Asn Gln Gln Lys Ser Thr 1 5 10 15

Asn Val Val Tyr Gln Ala His His Val Ser Arg Asn Lys Arg Gly Gln  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Val Val Gly Thr Arg Gly Gly Phe Arg Gly Cys Thr Val Trp Leu Thr 35 40 45

Gly Leu Ser Gly Ala Gly Lys Thr Thr Ile Ser Phe Ala Leu Glu Glu 50  $\,$  55  $\,$  60  $\,$ 

Tyr Leu Val Ser His Ala Ile Pro Cys Tyr Ser Leu Asp Gly Asp Asn 65 70 75 80

Val Arg His Gly Leu Asn Arg Asn Leu Gly Phe Ser Pro Gly Asp Arg 85 90 95

Glu Glu Asn Ile Arg Arg Ile Ala Glu Val Ala Lys Leu Phe Ala Asp  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105$ 

Ala Gly Leu Val Cys Ile Thr Ser Phe Ile Ser Pro Phe Ala Lys Asp 115 120 125

Arg Glu Asn Ala Arg Lys Ile His Glu Ser Ala Gly Leu Pro Phe Phe 130 135 140

Glu Ile Phe Val Asp Ala Pro Leu Asn Ile Cys Glu Ser Arg Asp Val 145 150 155 160

Lys Gly Leu Tyr Lys Lys Ala Arg Ala Gly Glu Ile Lys Gly Phe Thr  $165 \ \ 170 \ \ 175$ 

Gly Ile Asp Ser Asp Tyr Glu Lys Pro Glu Thr Pro Glu Arg Val Leu  $180 \hspace{1cm} 185 \hspace{1cm} 195 \hspace{1cm}$ 

Lys Thr Asn Leu Ser Thr Val Ser Asp Cys Val His Gln Val Val Glu 195  $\phantom{\bigg|}200\phantom{\bigg|}$ 

Leu Leu Gln Glu Gln Asn Ile Val Pro Tyr Thr Ile Ile Lys Asp Ile 210 215 220

His Glu Leu Phe Val Pro Glu Asn Lys Leu Asp His Val Arg Ala Glu 225 230 230 235 240

Ala Glu Thr Leu Pro Ser Leu Ser Ile Thr Lys Leu Asp Leu Gln Trp 245 250 255

Val Gln Val Leu Ser Glu Gly Trp Ala Thr Pro Leu Lys Gly Phe Met 260 265 270

Arg Glu Lys Glu Tyr Leu Gln Val Met His Phe Asp Thr Leu Leu Asp 275 280 285

Asp Gly Val Ile Asn Met Ser Ile Pro Ile Val Leu Pro Val Ser Ala 290 295 300

Glu Asp Lys Thr Arg Leu Glu Gly Cys Ser Lys Phe Val Leu Ala His 305 310 315 320

Gly Gly Arg Arg Val Ala Ile Leu Arg Asp Ala Glu Phe Tyr Glu His 325 330 335

Arg Lys Glu Glu Arg Cys Ser Arg Val Trp Gly Thr Thr Cys Thr Lys 340 345 350

His Pro His Ile Lys Met Val Met Glu Ser Gly Asp Trp Leu Val Gly 355 360 365

Gly Asp Leu Gln Val Leu Glu Lys Ile Arg Trp Asn Asp Gly Leu Asp 370 375 380

Gln Tyr Arg Leu Thr Pro Leu Glu Leu Lys Gln Lys Cys Lys Glu Met 385 390 395 400

Asn Ala Asp Ala Val Phe Ala Phe Gln Leu Arg Asn Pro Val His Asn 405  $\phantom{\bigg|}410\phantom{\bigg|}410\phantom{\bigg|}$ 

Gly His Ala Leu Leu Met Gln Asp Thr Arg Arg Arg Leu Leu Glu Arg 420 425 430

Gly Tyr Lys His Pro Val Leu Leu Leu His Pro Leu Gly Gly Trp Thr  $435 \hspace{1.5cm} 440 \hspace{1.5cm} 445$ 

Lys Asp Asp Asp Val Pro Leu Asp Trp Arg Met Lys Gln His Ala Ala 450  $\phantom{\bigg|}455\phantom{\bigg|}$ 

Val Leu Glu Glu Gly Val Leu Asp Pro Lys Ser Thr Ile Val Ala Ile 465 470 475 480

Phe Pro Ser Pro Met Leu Tyr Ala Gly Pro Thr Glu Val Gln Trp His 485 490 495

Cys Arg Ser Arg Met Ile Ala Gly Ala Asn Phe Tyr Ile Val Gly Arg 500 505 510

Asp Pro Ala Gly Met Pro His Pro Glu Thr Lys Lys Asp Leu Tyr Glu 515 520 525

Pro Thr His Gly Gly Lys Val Leu Ser Met Ala Pro Gly Leu Thr Ser 530 535 540

Val Glu Ile Ile Pro Phe Arg Val Ala Ala Tyr Asn Lys Ala Lys Lys 545 550 560

Ala Met Asp Phe Tyr Asp Leu Ala Arg His Asn Glu Phe Asp Phe Ile 565 570 575

Ser Gly Thr Arg Met Arg Lys Leu Ala Arg Glu Gly Glu Asn Pro Pro 580 585 590

Asp Gly Phe Met Ala Pro Lys Ala Trp Lys Val Leu Thr Asp Tyr Tyr 595 600 605

Arg Ser Leu Glu Lys Asn 610

210> 172

<211> 798 <212> PRT

<213> Homo sapiens

<400> 172

Met Asn Leu Gln Pro Ile Phe Trp Ile Gly Leu Ile Ser Ser Val Cys 1  $\phantom{\Big|}$  5  $\phantom{\Big|}$  10  $\phantom{\Big|}$  15

Cys Val Phe Ala Gln Thr Asp Glu Asn Arg Cys Leu Lys Ala Asn Ala 20 25 30

Lys Ser Cys Gly Glu Cys Ile Gln Ala Gly Pro Asn Cys Gly Trp Cys  $35 \hspace{1cm} 40 \hspace{1cm} 45$ Thr Asn Ser Thr Phe Leu Gln Glu Gly Met Pro Thr Ser Ala Arg Cys 50 60 Asp Asp Leu Glu Ala Leu Lys Lys Gly Cys Pro Pro Asp Asp Ile 65 70 75 80 Glu Asn Pro Arg Gly Ser Lys Asp Ile Lys Lys Asn Lys Asn Val Thr 85 90 95 Asn Arg Ser Lys Gly Thr Ala Glu Lys Leu Lys Pro Glu Asp Ile His  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110$ Gln Ile Gln Pro Gln Gln Leu Val Leu Arg Leu Arg Ser Gly Glu Pro 115 120 125 Gln Thr Phe Thr Leu Lys Phe Lys Arg Ala Glu Asp Tyr Pro Ile Asp 130 135 140 Leu Tyr Tyr Leu Met Asp Leu Ser Tyr Ser Met Lys Asp Asp Leu Glu 145 150 155 160 Asn Val Lys Ser Leu Gly Thr Asp Leu Met Asn Glu Met Arg Arg Ile 165 170 175Thr Ser Asp Phe Arg Ile Gly Phe Gly Ser Phe Val Glu Lys Thr Val 180  $$185\$ Met Pro Tyr Ile Ser Thr Thr Pro Ala Lys Leu Arg Asn Pro Cys Thr 195 200 205 Ser Glu Gln Asn Cys Thr Thr Pro Phe Ser Tyr Lys Asn Val Leu Ser 210 225 220 Leu Thr Asn Lys Gly Glu Val Phe Asn Glu Leu Val Gly Lys Gln Arg 225 230 235 240 Ile Ser Gly Asn Leu Asp Ser Pro Glu Gly Gly Phe Asp Ala Ile Met 245 250 255 Gln Val Ala Val Cys Gly Ser Leu Ile Gly Trp Arg Asn Val Thr Arg 260 265 270Leu Leu Val Phe Ser Thr Asp Ala Gly Phe His Phe Ala Gly Asp Gly 275  $\phantom{\bigg|}280\phantom{\bigg|}$  280  $\phantom{\bigg|}285\phantom{\bigg|}$ Lys Leu Gly Gly Ile Val Leu Pro Asn Asp Gly Gln Cys His Leu Glu 290 295 300 Asn Asn Met Tyr Thr Met Ser His Tyr Tyr Asp Tyr Pro Ser Ile Ala 305 310 315 320 His Leu Val Gln Lys Leu Ser Glu Asn Asn Ile Gln Thr Ile Phe Ala 325 330 335 Val Thr Glu Glu Phe Gln Pro Val Tyr Lys Glu Leu Lys Asn Leu Ile Page 269

340 345 350

Pro Lys Ser Ala Val Gly Thr Leu Ser Ala Asn Ser Ser Asn Val Ile 355 360 365 Gln Leu Ile Ile Asp Ala Tyr Asn Ser Leu Ser Ser Glu Val Ile Leu  $370 \hspace{1cm} 375 \hspace{1cm} 380$ Glu Asn Gly Lys Leu Ser Glu Gly Val Thr Ile Ser Tyr Lys Ser Tyr 385 390 395 400 Cys Lys Asn Gly Val Asn Gly Thr Gly Glu Asn Gly Arg Lys Cys Ser 405 410 415Asn Ile Ser Ile Gly Asp Glu Val Gln Phe Glu Ile Ser Ile Thr Ser 420 425 430 Asn Lys Cys Pro Lys Lys Asp Ser Asp Ser Phe Lys Ile Arg Pro Leu 435 440 445 Gly Phe Thr Glu Glu Val Glu Val Ile Leu Gln Tyr Ile Cys Glu Cys 450 455 460 Glu Cys Gln Ser Glu Gly Ile Pro Glu Ser Pro Lys Cys His Glu Gly 465 470 475 480 Asn Gly Thr Phe Glu Cys Gly Ala Cys Arg Cys Asn Glu Gly Arg Val 485 490 495 Gly Arg His Cys Glu Cys Ser Thr Asp Glu Val Asn Ser Glu Asp Met 500 505 510 Asp Ala Tyr Cys Arg Lys Glu Asn Ser Ser Glu Ile Cys Ser Asn Asn 515 520 525 Gly Glu Cys Val Cys Gly Gln Cys Val Cys Arg Lys Arg Asp Asn Thr 530 535 540 Asn Glu Ile Tyr Ser Gly Lys Phe Cys Glu Cys Asp Asn Phe Asn Cys 545 550 560 Asp Arg Ser Asn Gly Leu Ile Cys Gly Gly Asn Gly Val Cys Lys Cys 565 570 575 Arg Val Cys Glu Cys Asn Pro Asn Tyr Thr Gly Ser Ala Cys Asp Cys 580 585 590 Ser Leu Asp Thr Ser Thr Cys Glu Ala Ser Asn Gly Gln Ile Cys Asn 595 600 605 Gly Arg Gly Ile Cys Glu Cys Gly Val Cys Lys Cys Thr Asp Pro Lys 610 620 Phe Gln Gly Gln Thr Cys Glu Met Cys Gln Thr Cys Leu Gly Val Cys 625 630 635 640

Ala Glu His Lys Glu Cys Val Gln Cys Arg Ala Phe Asn Lys Gly Glu 645 650 655

Lys Lys Asp Thr Cys Thr Gln Glu Cys Ser Tyr Phe Asn Ile Thr Lys  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670 \hspace{1.5cm}$ 

Val Glu Ser Arg Asp Lys Leu Pro Gln Pro Val Gln Pro Asp Pro Val 675 680 685

Ser His Cys Lys Glu Lys Asp Val Asp Asp Cys Trp Phe Tyr Phe Thr 690 700

Tyr Ser Val Asn Gly Asn Asn Glu Val Met Val His Val Val Glu Asn 705 710 715 720

Pro Glu Cys Pro Thr Gly Pro Asp Ile Ile Pro Ile Val Ala Gly Val 725  $\phantom{-}730\phantom{0}$  735

Val Ala Gly Ile Val Leu Ile Gly Leu Ala Leu Leu Leu Ile Trp Lys 740 745 750

Leu Leu Met Ile Ile His Asp Arg Arg Glu Phe Ala Lys Phe Glu Lys  $755 \hspace{1.5cm} 760 \hspace{1.5cm} 765$ 

Glu Lys Met Asn Ala Lys Trp Asp Thr Gly Glu Asn Pro Ile Tyr Lys 770 780

Ser Ala Val Thr Thr Val Val Asn Pro Lys Tyr Glu Gly Lys 785 790 795

<210> 173

<211> 502

<212> PRT

<213> Homo sapiens

<400> 173

Met Ala Ser Lys Lys Leu Gly Ala Asp Phe His Gly Thr Phe Ser Tyr 1 10 15

Leu Asp Asp Val Pro Phe Lys Thr Gly Asp Lys Phe Lys Thr Pro Ala 20 25 30

Lys Val Gly Leu Pro Ile Gly Phe Ser Leu Pro Asp Cys Leu Gln Val 35 40 45

Val Arg Glu Val Gln Tyr Asp Phe Ser Leu Glu Lys Lys Thr Ile Glu 50 55 60

Trp Ala Glu Glu Ile Lys Lys Ile Glu Glu Ala Glu Arg Glu Ala Glu 65 70 75 80

Cys Lys Ile Ala Glu Ala Glu Ala Lys Val Asn Ser Lys Ser Gly Pro  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Glu Gly Asp Ser Lys Met Ser Phe Ser Lys Thr His Ser Thr Ala Thr  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110 \hspace{1.5cm} .$ 

Met Pro Pro Pro Ile Asn Pro Ile Leu Ala Ser Leu Gln His Asn Ser 115 120 125

Ile Leu Thr Pro Thr Arg Val Ser Ser Ser Ala Thr Lys Gln Lys Val

Leu Ser Pro Pro His Ile Lys Ala Asp Phe Asn Leu Ala Asp Phe Glu 145 150 155 160

Cys Glu Glu Asp Pro Phe Asp Asn Leu Glu Leu Lys Thr Ile Asp Glu 165 170 175

Lys Glu Glu Leu Arg Asn Ile Leu Val Gly Thr Thr Gly Pro Ile Met 180  $$185\$ 

Ala Gln Leu Leu Asp Asn Asn Leu Pro Arg Gly Gly Ser Gly Ser Val

Leu Gln Asp Glu Glu Val Leu Ala Ser Leu Glu Arg Ala Thr Leu Asp 210 215 220

Phe Lys Pro Leu His Lys Pro Asn Gly Phe Ile Thr Leu Pro Gln Leu 225 230 230 240

Gly Asn Cys Glu Lys Met Ser Leu Ser Ser Lys Val Ser Leu Pro Pro 245 250 255

Ile Pro Ala Val Ser Asn Ile Lys Ser Leu Ser Phe Pro Lys Leu Asp 260 265 270

Ser Asp Asp Ser Asn Gln Lys Thr Ala Lys Leu Ala Ser Thr Phe His 275 280 285

Ser Thr Ser Cys Leu Arg Asn Gly Thr Phe Gln Asn Ser Leu Lys Pro 290 295 300

Ser Thr Gln Ser Ser Ala Ser Glu Leu Asn Gly His His Thr Leu Gly 305 310 315 320

Leu Ser Ala Leu Asn Leu Asp Ser Gly Thr Glu Met Pro Ala Leu Thr  $325 \hspace{1.5cm} 330 \hspace{1.5cm} 335$ 

Ser Ser Gln Met Pro Ser Leu Ser Val Leu Ser Val Cys Thr Glu Glu 340 345 350

Val Ser Gln Val Pro Asn Met Pro Ser Cys Pro Gln Ala Tyr Ser Glu 370 375 380

Leu Gln Met Leu Ser Pro Ser Glu Arg Gln Cys Val Glu Thr Val Val 385  $\phantom{\bigg|}390\phantom{\bigg|}395\phantom{\bigg|}395\phantom{\bigg|}$ 

Asn Met Gly Tyr Ser Tyr Glu Cys Val Leu Arg Ala Met Lys Lys Lys 405 410 415

Gly Glu Asn Ile Glu Gln Ile Leu Asp Tyr Leu Phe Ala His Gly Gln 420 425 430

Leu Cys Glu Lys Gly Phe Asp Pro Leu Leu Val Glu Glu Ala Leu Glu 435 440 445

Ser Lys Phe Lys Glu Met Gly Phe Glu Leu Lys Asp Ile Lys Glu Val 465 470 475 480

Leu Leu His Asn Asn Asp Gln Asp Asn Ala Leu Glu Asp Leu Met 485 490 495

Ala Arg Ala Gly Ala Ser 500

<210>

<213> Homo sapiens

Met Ser Asn Asn Gly Leu Asp Ile Gln Asp Lys Pro Pro Ala Pro Pro 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Met Arg Asn Thr Ser Thr Met Ile Gly Val Gly Ser Lys Asp Ala Gly 20 25 30

Thr Leu Asn His Gly Ser Lys Pro Leu Pro Pro Asn Pro Glu Glu Lys 35 40 45

Lys Lys Lys Asp Arg Phe Tyr Arg Ser Ile Leu Pro Gly Asp Lys Thr 50 60

Asn Lys Lys Glu Lys Glu Arg Pro Glu Ile Ser Leu Pro Ser Asp 65 70 75 80

Phe Glu His Thr Ile His Val Gly Phe Asp Ala Val Thr Gly Glu Phe 85 90 95

Thr Gly Met Pro Glu Gln Trp Ala Arg Leu Leu Gln Thr Ser Asn Ile 100 105 110

Thr Lys Ser Glu Gln Lys Lys Asn Pro Gln Ala Val Leu Asp Val Leu 115 120 125

Glu Phe Tyr Asn Ser Lys Lys Thr Ser Asn Ser Gln Lys Tyr Met Ser 130  $^{\circ}$  135  $^{\circ}$  140

Phe Thr Asp Lys Ser Ala Glu Asp Tyr Asn Ser Ser Asn Ala Leu Asn 145 150 160

Val Lys Ala Val Ser Glu Thr Pro Ala Val Pro Pro Val Ser Glu Asp 165 170 175

Glu Asp Asp Asp Asp Asp Asp Ala Thr Pro Pro Pro Val Ile Ala Pro 180 185 190

Arg Pro Glu His Thr Lys Ser Val Tyr Thr Arg Ser Val Ile Glu Pro 195  $\phantom{\bigg|}200\phantom{\bigg|}$ 

Leu Pro Val Thr Pro Thr Arg Asp Val Ala Thr Ser Pro Ile Ser Pro 210 215 220

Thr Glu Asn Asn Thr Thr Pro Pro Asp Ala Leu Thr Arg Asn Thr Glu 225 230 235 240

Lys Gln Lys Lys Lys Pro Lys Met Ser Asp Glu Glu Ile Leu Glu Lys 245 250 255

Leu Arg Ser Ile Val Ser Val Gly Asp Pro Lys Lys Lys Tyr Thr Arg 260 265 270

Phe Glu Lys Ile Gly Gln Gly Ala Ser Gly Thr Val Tyr Thr Ala Met 275 280 285

Asp Val Ala Thr Gly Gln Glu Val Ala le Lys Gln Met Asn Leu Gln 290 295 300

Gln Gln Pro Lys Lys Glu Leu Ile Ile Asn Glu Ile Leu Val Met Arg 305 310 315 320

Glu Asn Lys Asn Pro Asn Ile Val Asn Tyr Leu Asp Ser Tyr Leu Val 325 330 335

Gly Asp Glu Leu Trp Val Val Met Glu Tyr Leu Ala Gly Gly Ser Leu 340 345 350

Thr Asp Val Val Thr Glu Thr Cys Met Asp Glu Gly Gln Ile Ala Ala 355 360 365

Val Cys Arg Glu Cys Leu Gln Ala Leu Glu Phe Leu His Ser Asn Gln 370 375 380

Val Ile His Arg Asp Ile Lys Ser Asp Asn Ile Leu Leu Gly Met Asp 385 390 400

Gly Ser Val Lys Leu Thr Asp Phe Gly Phe Cys Ala Gln Ile Thr Pro 405 410 415

Glu Gln Ser Lys Arg Ser Thr Met Val Gly Thr Pro Tyr Trp Met Ala 420 425 430

Pro Glu Val Val Thr Arg Lys Ala Tyr Gly Pro Lys Val Asp Ile Trp 435 440 445

Ser Leu Gly Ile Met Ala Ile Glu Met Ile Glu Gly Glu Pro Pro Tyr 450 460

Leu Asn Glu Asn Pro Leu Arg Ala Leu Tyr Leu Ile Ala Thr Asn Gly 465 470 475 480

Thr Pro Glu Leu Gln Asn Pro Glu Lys Leu Ser Ala Ile Phe Arg Asp 485 490 495

Phe Leu Asn Arg Cys Leu Asp Met Asp Val Glu Lys Arg Gly Ser Ala 500 505 510

Lys Glu Leu Leu Gln His Gln Phe Leu Lys Ile Ala Lys Pro Leu Ser 515 520 525

Ser Leu Thr Pro Leu Ile Ala Ala Ala Lys Glu Ala Thr Lys Asn Asn 530 540

545

<210> 175

<211> 1366 <212> PRT

<213> Homo sapiens

<400> 175

Met Ser Arg Gln Ser Thr Leu Tyr Ser Phe Phe Pro Lys Ser Pro Ala  $1 \hspace{1.5cm} 5 \hspace{1.5cm} 10 \hspace{1.5cm} 15$ 

Leu Ser Asp Ala Asn Lys Ala Ser Ala Arg Ala Ser Arg Glu Gly Gly 20 25 30

Arg Ala Ala Ala Pro Gly Ala Ser Pro Ser Pro Gly Gly Asp Ala 35 40 45

Ala Trp Ser Glu Ala Gly Pro Gly Pro Arg Pro Leu Ala Arg Ser Ala 50 55 60

Ser Pro Pro Lys Ala Lys Asn Leu Asn Gly Gly Leu Arg Arg Ser Val 65 70 75 80

Ala Pro Ala Ala Pro Thr Ser Cys Asp Phe Ser Pro Gly Asp Leu Val $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Trp Ala Lys Met Glu Gly Tyr Pro Trp Trp Pro Cys Leu Val Tyr Asn  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105$ 

His Pro Phe Asp Gly Thr Phe Ile Arg Glu Lys Gly Lys Ser Val Arg 115 120 125

Val His Val Gln Phe Phe Asp Asp Ser Pro Thr Arg Gly Trp Val Ser 130 140

Lys Arg Leu Leu Lys Pro Tyr Thr Gly Ser Lys Ser Lys Glu Ala Gln 145 150 160

Lys Gly Gly His Phe Tyr Ser Ala Lys Pro Glu Ile Leu Arg Ala Met 165 170 175

Gln Arg Ala Asp Glu Ala Leu Asn Lys Asp Lys Ile Lys Arg Leu Glu 180 185 190

Leu Ala Val Cys Asp Glu Pro Ser Glu Pro Glu Glu Glu Glu Glu Met 195 200 205

Glu Val Gly Thr Thr Tyr Val Thr Asp Lys Ser Glu Glu Asp Asn Glu 210 215 220

Ile Glu Ser Glu Glu Glu Val Gln Pro Lys Thr Gln Gly Ser Arg Arg 225 230 240

Ser Ser Arg Gln Ile Lys Lys Arg Arg Val Ile Ser Asp Ser Glu Ser 245 250 255

Asp Ile Gly Gly Ser Asp Val Glu Phe Lys Pro Asp Thr Lys Glu Glu 260 265 270

Gly Ser Ser Asp Glu Ile Ser Ser Gly Val Gly Asp Ser Glu Ser Glu 275 280 285

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Gly Leu Asn Ser Pro Val Lys Val Ala Arg Lys Arg Lys Arg Met Val 290 295 300 Thr Gly Asn Gly Ser Leu Lys Arg Lys Ser Ser Arg Lys Glu Thr Pro 305 310 315 320 Ser Ala Thr Lys Gln Ala Thr Ser Ile Ser Ser Glu Thr Lys Asn Thr 325 330 335Thr Leu Glu Trp Leu Lys Glu Glu Lys Arg Arg Asp Glu His Arg Arg 370 375 380Arg Pro Asp His Pro Asp Phe Asp Ala Ser Thr Leu Tyr Val Pro Glu 385 390 395 400 Asp Phe Leu Asn Ser Cys Thr Pro Gly Met Arg Lys Trp Trp Gln Ile 405 410 415 Tyr Glu Leu Tyr His Met Asp Ala Leu Ile Gly Val Ser Glu Leu Gly 435  $\phantom{\bigg|}$  440  $\phantom{\bigg|}$  445 Leu Val Phe Met Lys Gly Asn Trp Ala His Ser Gly Phe Pro Glu Ile 450 455 460 Ala Phe Gly Arg Tyr Ser Asp Ser Leu Val Gln Lys Gly Tyr Lys Val 465 470 480 Ala Arg Val Glu Gln Thr Glu Thr Pro Glu Met Met Glu Ala Arg Cys 485 490 495Arg Lys Met Ala His Ile Ser Lys Tyr Asp Arg Val Val Arg Arg Glu
500 505 510 Ile Cys Arg Ile Ile Thr Lys Gly Thr Gln Thr Tyr Ser Val Leu Glu 515 520 525 Gly Asp Pro Ser Glu Asn Tyr Ser Lys Tyr Leu Leu Ser Leu Lys Glu 530 535 540 Lys Glu Glu Asp Ser Ser Gly His Thr Arg Ala Tyr Gly Val Cys Phe 545 550 560 Val Asp Thr Ser Leu Gly Lys Phe Phe Ile Gly Gln Phe Ser Asp Asp 565 570 575 Arg His Cys Ser Arg Phe Arg Thr Leu Val Ala His Tyr Pro Pro Val 580 585 590Gln Val Leu Phe Glu Lys Gly Asn Leu Ser Lys Glu Thr Lys Thr Ile Page 276

600 60

Leu Lys Ser Ser Leu Ser Cys Ser Leu Gln Glu Gly Leu Ile Pro Gly 610 620 Ser Gln Phe Trp Asp Ala Ser Lys Thr Leu Arg Thr Leu Leu Glu Glu 625 630 635 640 Glu Tyr Phe Arg Glu Lys Leu Ser Asp Gly Ile Gly Val Met Leu Pro 645 650 655 Gln Val Leu Lys Gly Met Thr Ser Glu Ser Asp Ser Ile Gly Leu Thr  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670 \hspace{1.5cm}$ Pro Gly Glu Lys Ser Glu Leu Ala Leu Ser Ala Leu Gly Gly Cys Val675  $\phantom{0}$  685  $\phantom{0}$  685 Phe Tyr Leu Lys Lys Cys Leu Ile Asp Gln Glu Leu Leu Ser Met Ala 690 695 700 Asn Phe Glu Glu Tyr Ile Pro Leu Asp Ser Asp Thr Val Ser Thr Thr 705 710 715 720Arg Ser Gly Ala Ile Phe Thr Lys Ala Tyr Gln Arg Met Val Leu Asp 725 730 735Ala Val Thr Leu Asn Asn Leu Glu Ile Phe Leu Asn Gly Thr Asn Gly 740 745 750Ser Thr Glu Gly Thr Leu Leu Glu Arg Val Asp Thr Cys His Thr Pro  $755 \hspace{1.5cm} 760 \hspace{1.5cm} 765$ Phe Gly Lys Arg Leu Leu Lys Gln Trp Leu Cys Ala Pro Leu Cys Asn 770 775 780 His Tyr Ala Ile Asn Asp Arg Leu Asp Ala Ile Glu Asp Leu Met Val 785 790 795 800 Val Pro Asp Lys Ile Ser Glu Val Val Glu Leu Leu Lys Lys Leu Pro 805 810 815 Asp Leu Glu Arg Leu Leu Ser Lys Ile His Asn Val Gly Ser Pro Leu 820 825 830 Lys Ser Gln Asn His Pro Asp Ser Arg Ala Ile Met Tyr Glu Glu Thr 835 840 845 Thr Tyr Ser Lys Lys Lys Ile Ile Asp Phe Leu Ser Ala Leu Glu Gly 850 855 860 Phe Lys Val Met Cys Lys Ile Ile Gly Ile Met Glu Glu Val Ala Asp 865 870 875 880 Gly Phe Lys Ser Lys Ile Leu Lys Gln Val Ile Ser Leu Gln Thr Lys 885 890 895 Asn Pro Glu Gly Arg Phe Pro Asp Leu Thr Val Glu Leu Asn Arg Trp 900 905 910

Asp Thr Ala Phe Asp His Glu Lys Ala Arg Lys Thr Gly Leu Ile Thr 915 920 925

Pro Lys Ala Gly Phe Asp Ser Asp Tyr Asp Gln Ala Leu Ala Asp Ile 930 940

Arg Glu Asn Glu Gln Ser Leu Leu Glu Tyr Leu Glu Lys Gln Arg Asn 945 950 955 960

Arg Ile Gly Cys Arg Thr Ile Val Tyr Trp Gly Ile Gly Arg Asn Arg 965 970 975

Tyr Gln Leu Glu Ile Pro Glu Asn Phe Thr Thr Arg Asn Leu Pro Glu 980 985 990

Glu Tyr Glu Leu Lys Ser Thr Lys Lys Gly Cys Lys Arg Tyr Trp Thr 995 1000 1005

Lys Thr Ile Glu Lys Lys Leu Ala Asn Leu Ile Asn Ala Glu Glu 1010 1015 1020

Arg Arg Asp Val Ser Leu Lys Asp Cys Met Arg Arg Leu Phe Tyr 1025 1035

Asn Phe Asp Lys Asn Tyr Lys Asp Trp Gln Ser Ala Val Glu Cys 1040 1050

Ile Ala Val Leu Asp Val Leu Leu Cys Leu Ala Asn Tyr Ser Arg 1055 1066

Gly Gly Asp Gly Pro Met Cys Arg Pro Val Ile Leu Leu Pro Glu 1070 1075 1080

Asp Thr Pro Pro Phe Leu Glu Leu Lys Gly Ser Arg His Pro Cys 1085 1095

Ile Thr Lys Thr Phe Phe Gly Asp Asp Phe Ile Pro Asn Asp Ile 1100  $$1105\$ 

Leu Ile Gly Cys Glu Glu Glu Glu Glu Glu Asn Gly Lys Ala Tyr 1115 1120 1125

Cys Val Leu Val Thr Gly Pro Asn Met Gly Gly Lys Ser Thr Leu 1130 1140

Met Arg Gln Ala Gly Leu Leu Ala Val Met Ala Gln Met Gly Cys 1145 1150 1155

Tyr Val Pro Ala Glu Val Cys Arg Leu Thr Pro Ile Asp Arg Val 1160  $\dot{}^{\circ}$  1165 1170

Phe Thr Arg Leu Gly Ala Ser Asp Arg Ile Met Ser Gly Glu Ser 1175 1180 1185

Thr Phe Phe Val Glu Leu Ser Glu Thr Ala Ser Ile Leu Met His 1190 1195 1200

Ala Thr Ala His Ser Leu Val Leu Val Asp Glu Leu Gly Arg Gly 1205 1210 1215

Thr Ala Thr Phe Asp Gly Thr Ala Ile Ala Asn Ala Val Val Lys  $1220 \hspace{1.5cm} 1225 \hspace{1.5cm} 1230$ 

Glu Leu Ala Glu Thr Ile Lys Cys Arg Thr Leu Phe Ser Thr His 1235 1240 1245

Tyr His Ser Leu Val Glu Asp Tyr Ser Gln Asn Val Ala Val Arg 1250 1255 1260

Leu Gly His Met Ala Cys Met Val Glu Asn Glu Cys Glu Asp Pro 1265 1270 1275

Ser Gln Glu Thr Ile Thr Phe Leu Tyr Lys Phe Ile Lys Gly Ala 1280 1285 1290

Cys Pro Lys Ser Tyr Gly Phe Asn Ala Ala Arg Leu Ala Asn Leu 1295 1300 1305

Pro Glu Glu Val Ile Gln Lys Gly His Arg Lys Ala Arg Glu Phe 1310 1315 1320

Glu Lys Met Asn Gln Ser Leu Arg Leu Phe Arg Glu Val Cys Leu 1325 1330 1335

Ala Ser Glu Arg Ser Thr Val Asp Ala Glu Ala Val His Lys Leu 1340 1350 1350

Leu Thr Leu Ile Lys Glu Leu 1355 136

<210> 176 <211> 398 <212> PRT

<213> Homo sapiens

<400> 176

Met Gln Ser Glu Arg Gly Ile Thr Ile Asp Ile Ser Leu Trp Lys Phe 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Glu Thr Ser Lys Tyr Tyr Val Thr Ile Ile Asp Ala Pro Gly His Arg  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Asp Phe Ile Gln Asn Met Ile Thr Gly Thr Ser Gln Ala Asp Cys Ala 35  $\phantom{\bigg|}40\phantom{\bigg|}40\phantom{\bigg|}45\phantom{\bigg|}$ 

Val Leu Ile Val Ala Ala Gly Val Gly Glu Phe Glu Ala Gly Ile Ser 50 60

Lys Asn Gly Gln Thr Arg Glu His Ala Leu Leu Ala Tyr Thr Leu Gly 65 70 75 80

Val Lys Gln Leu Ile Val Gly Val Asn Lys Met Asp Ser Thr Glu Pro 85 90 95

Pro Tyr Ser Gln Lys Arg Tyr Glu Glu Ile Val Lys Glu Val Ser Thr  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105$ 

Tyr Ile Lys Lys Ile Gly Tyr Asn Pro Asp Thr Val Ala Phe Val Pro  $115^{\circ}$  120 125

Ile Ser Gly Trp Asn Gly Asp Asn Met Leu Glu Pro Ser Ala Asn Met
130 135

Pro Trp Phe Lys Gly Trp Lys Val Thr Arg Lys Asp Gly Asn Ala Ser 145  $\phantom{\bigg|}$  150  $\phantom{\bigg|}$  155  $\phantom{\bigg|}$  160

Gly Thr Thr Leu Leu Glu Ala Leu Asp Cys Ile Leu Pro Pro Thr Arg 165 170 175

Pro Thr Asp Lys Pro Leu Gly Leu Pro Leu Gln Asp Val Tyr Lys Ile 180  $$185\$ 

Gly Gly Ile Gly Thr Val Pro Val Gly Arg Val Glu Thr Gly Val Leu 195 200 205

Lys Pro Gly Met Val Val Thr Phe Gly Pro Val Asn Val Thr Thr Glu 210 215 220

Val Lys Ser Val Glu Met His His Glu Ala Leu Gly Glu Ala Leu Pro 225 230 235 240

Gly Asp Asn Val Gly Phe Asn Val Lys Asn Val Ser Val Lys Asp Val 245 250 255

Arg Arg Gly Asn Val Ala Gly Asp Ser Lys Asn Asp Pro Pro Met Glu 260 265 270

Ala Ala Gly Phe Pro Ala Gln Val Ile Ile Leu Asn His Pro Gly Gln 275 280 285

Ile Ser Ala Gly Tyr Ala Pro Val Leu Asp Cys His Thr Ala His Ile 290 295 300

Ala Cys Lys Phe Ala Glu Leu Lys Glu Lys Ile Asp Arg Arg Ser Gly 305 310 315 320

Lys Lys Leu Glu Asp Gly Pro Lys Phe Leu Lys Ser Gly Asp Ala Ala 325 330 335

Ile Val Asp Met Val Pro Gly Lys Pro Met Cys Val Glu Ser Phe Ser 340 345 350

Asp Tyr Pro Pro Leu Gly Cys Phe Ala Val Arg Asp Met Arg Gln Thr 355 360 365

Val Ala Val Gly Val Ile Lys Ala Val Asp Lys Lys Ala Ala Gly Ala 370 375 380

Gly Lys Val Thr Lys Ser Ala Gln Lys Ala Gln Lys Ala Lys 385 390 395

<210> 177

<211> 334 <212> PRT

<213> Homo sapiens

<400> 177

Met Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Glu Glu Glu 1 5 10 15

Ala Thr Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val  $20 \hspace{1cm} 25 \hspace{1cm} 30 \hspace{1cm}$ 

Gly Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu 35 40 45

Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met 50 60

Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala 65 70 75 80

Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Thr 85 90 95

Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110 \hspace{1.5cm}$ 

Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr  $115 \ \ 125 \ \ \ 125$ 

Ser Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu 130 135 140

Thr Tyr Val Thr Trp Lys Leu Ser Gly Leu Pro Lys His Arg Val Ile 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ 

Gly Ser Gly Cys Asn Leu Asp Ser Ala Arg Phe Arg Tyr Leu Met Ala 165 170 175

Glu Lys Leu Gly Ile His Pro Ser Ser Cys His Gly Trp Ile Leu Gly  $180 \hspace{1cm} 185 \hspace{1cm} 190$ 

Glu His Gly Asp Ser Ser Val Ala Val Trp Ser Gly Val Asn Val Ala  $^{\star}$  195 200 205

Gly Val Ser Leu Gln Glu Leu Asn Pro Glu Met Gly Thr Asp Asn Asp 210 215 220

Ser Glu Asn Trp Lys Glu Val His Lys Met Val Val Glu Ser Ala Tyr 225 230 235 240

Glu Val Ile Lys Leu Lys Gly Tyr Thr Asn Trp Ala Ile Gly Leu Ser 245 250 255

Val Ala Asp Leu Ile Glu Ser Met Leu Lys Asn Leu Ser Arg Ile His 260 265 270

Pro Val Ser Thr Met Val Lys Gly Met Tyr Gly Ile Glu Asn Glu Val 275 280 285

Phe Leu Ser Leu Pro Cys Ile Leu Asn Ala Arg Gly Leu Thr Ser Val 290 295 300

Ile Asn Gln Lys Leu Lys Asp Asp Glu Val Ala Gln Leu Lys Lys Ser 305 310 315

Ala Asp Thr Leu Trp Asp Ile Gln Lys Asp Leu Lys Asp Leu 325 330

<210> 178

<211> 364

212> PRT

<213> Homo sapiens

<400> 178

Met Tyr Leu Ser Arg Phe Leu Ser Ile His Ala Leu Trp Val Thr Val 1 5 10 15

Ser Ser Val Met Gln Pro Tyr Pro Leu Val Trp Gly His Tyr Asp Leu 20 25 30

Cys Lys Thr Gln Ile Tyr Thr Glu Glu Gly Lys Val Trp Asp Tyr Met  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Ala Cys Gln Pro Glu Ser Thr Asp Met Thr Lys Tyr Leu Lys Val Lys 50 60

Leu Asp Pro Pro Asp Ile Thr Cys Gly Asp Pro Pro Glu Thr Phe Cys 65 70 . 80

Ala Met Gly Asn Pro Tyr Met Cys Asn Asn Glu Cys Asp Ala Ser Thr 85 90 95

Pro Glu Leu Ala His Pro Pro Glu Leu Met Phe Asp Phe Glu Gly Arg 100  $\phantom{-}105\phantom{0}$  110

His Pro Ser Thr Phe Trp Gln Ser Ala Thr Trp Lys Glu Tyr Pro Lys 115 120 125

Pro Leu Gln Val Asn Ile Thr Leu Ser Trp Ser Lys Thr Ile Glu Leu 130 135 140

Thr Asp Asn Ile Val Ile Thr Phe Glu Ser Gly Arg Pro Asp Gln Met 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ 

Ile Leu Glu Lys Ser Leu Asp Tyr Gly Arg Thr Trp Gln Pro Tyr Gln 165 170 175

Tyr Tyr Ala Thr Asp Cys Leu Asp Ala Phe His Met Asp Pro Lys Ser 180 185 190

Val Lys Asp Leu Ser Gln His Thr Val Leu Glu Ile Ile Cys Thr Glu 195 200 205

Glu Tyr Ser Thr Gly Tyr Thr Thr Asn Ser Lys Ile Ile His Phe Glu 210 215 220

Ile Lys Asp Arg Phe Ala Phe Phe Ala Gly Pro Arg Leu Arg Asn Met 225 230 235 240

Ala Ser Leu Tyr Gly Gln Leu Asp Thr Thr Lys Lys Leu Arg Asp Phe  $\phantom{-}245\phantom{0}$ 

Phe Thr Val Thr Asp Leu Arg Ile Arg Leu Leu Arg Pro Ala Val Gly 260 265 270

Glu Ile Phe Val Asp Glu Leu His Leu Ala Arg Tyr Phe Tyr Ala Ile  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285$ 

Ser Asp Ile Lys Val Arg Gly Arg Cys Lys Cys Asn Leu His Ala Thr 290 300 .

Val Cys Val Tyr Asp Asn Ser Lys Leu Thr Cys Glu Cys Glu His Asn 305 310 315 320

Thr Thr Gly Pro Asp Cys Gly Lys Cys Lys Lys Asn Tyr Gln Gly Arg 325 330 335

Pro Trp Ser Pro Gly Ser Tyr Leu Pro Ile Pro Lys Gly Thr Ala Asn 340 345 350

Thr Cys Ile Pro Ser Ile Ser Ser Ile Gly Ser Lys 355 360

<210> 179

<211> 416

<212> PRT <213> Homo sapiens

<400> 179

Met His Thr Asp Pro Asp Tyr Ser Ala Ala Tyr Val Val Ile Glu Thr 1  $\phantom{\Big|}$  5  $\phantom{\Big|}$  10  $\phantom{\Big|}$  15

Asp Ala Glu Asp Gly Ile Lys Gly Cys Gly Ile Thr Phe Thr Leu Gly 20 25 30

Lys Gly Thr Glu Val Val Val Cys Ala Val Asn Ala Leu Ala His His  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Val Leu Asn Lys Asp Leu Lys Asp Ile Val Gly Asp Phe Arg Gly Phe 50 60

Tyr Arg Gln Leu Thr Ser Asp Gly Gln Leu Arg Trp Ile Gly Pro Glu 65  $\phantom{000}70\phantom{000}$  70  $\phantom{0000}75\phantom{000}$  80

Lys Gly Val Val His Leu Ala Thr Ala Ala Val Leu Asn Ala Val Trp  $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Asp Leu Trp Ala Lys Gln Glu Gly Lys Pro Val Trp Lys Leu Leu Val 100 105 110

Asp Met Asp Pro Arg Met Leu Val Ser Cys Ile Asp Phe Arg Tyr Ile 115 120 125

Thr Asp Val Leu Thr Glu Glu Asp Ala Leu Glu Ile Leu Gln Lys Gly 130 135 140

Gln Ile Gly Lys Lys Glu Arg Glu Lys Gln Met Leu Ala Gln Gly Tyr 145 150 155 160

Pro Ala Tyr Thr Ser Cys Ala Trp Leu Gly Tyr Ser Asp Asp Thr 165 170 175

Leu Lys Gln Leu Cys Ala Gln Ala Leu Lys Asp Gly Trp Thr Arg Phe 180 185 190

Lys Val Lys Val Gly Ala Asp Leu Gln Asp Asp Met Arg Arg Cys Gln 195 200 205

Ile Ile Arg Asp Met Ile Gly Pro Glu Lys Thr Leu Met Met Asp Ala 210 215 220

Ala Lys Phe Lys Pro Leu Trp Ile Glu Glu Pro Thr Ser Pro Asp Asp 245 250 255

Ile Leu Gly His Ala Thr Ile Ser Lys Ala Leu Val Pro Leu Gly Ile 260 265 270

Gly Ile Ala Thr Gly Glu Gln Cys His Asn Arg Val Ile Phe Lys Gln 275 280 285

Leu Leu Gln Ala Lys Ala Leu Gln Phe Leu Gln Ile Asp Ser Cys Arg 290 295 300

Leu Gly Ser Val Asn Glu Asn Leu Ser Val Leu Leu Met Ala Lys Lys 305 310 315 320

Leu Val Gln His Leu Ile Ile Phe Asp Tyr Ile Ser Val Ser Ala Ser 340  $\phantom{\bigg|}345\phantom{\bigg|}$ 

Leu Glu Asn Arg Val Cys Glu Tyr Val Asp His Leu His Glu His Phe 355 360 365

Lys Tyr Pro Val Met Ile Gln Arg Ala Ser Tyr Met Pro Pro Lys Asp 370 375 380

Pro Gly Tyr Ser Thr Glu Met Lys Glu Glu Ser Val Lys Lys His Gln 385 390 400

Tyr Pro Asp Gly Glu Val Trp Lys Lys Leu Leu Pro Ala Gln Glu Asn 405 410 415

<210> 180

<211> 89

<212> PRT

<213> Homo sapiens

<400> 180

Met Ser Ser Gln Gln Gln Lys Gln Pro Cys Ile Pro Pro Pro Gln Leu 1 5 10 15

Gln Gln Gln Val Lys Gln Pro Cys Gln Pro Pro Pro Gln Glu Pro 20 25 30

Cys Ile Pro Lys Thr Lys Glu Pro Cys His Pro Lys Val Pro Glu Pro 35 40 40 45

Cys His Pro Lys Val Pro Glu Pro Cys Gln Pro Lys Leu Pro Glu Pro 50 60

Cys His Pro Lys Val Pro Glu Pro Cys Pro Ser Ile Val Thr Pro Ala 65 70 75 80

Page 284

Pro Ala Gln Gln Lys Thr Lys Gln Lys 85

<210> 181

<211> 25

<212> PRT

<213> Homo sapiens

<400> 181

Met Ala Arg Ser Leu Leu Pro Leu Gln Ile Leu Leu Leu Ser Leu 1 10 15

Ala Leu Glu Thr Ala Gly Glu Glu Ala Gln Gly Asp Lys Ile Ile Asp 20 25 30

Gly Ala Pro Cys Ala Arg Gly Ser His Pro Trp Gln Val Ala Leu Leu  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Ser Gly Asn Gln Leu His Cys Gly Gly Val Leu Val Asn Glu Arg Trp 50 60

Val Leu Thr Ala Ala His Cys Lys Met Asn Glu Tyr Thr Val His Leu 65 70 75 80

Gly Ser Asp Thr Leu Gly Asp Arg Arg Ala Gln Arg Ile Lys Ala Ser 90 95

Lys Ser Phe Arg His Pro Gly Tyr Ser Thr Gln Thr His Val Asn Asp  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105$ 

Leu Met Leu Val Lys Leu Asn Ser Gln Ala Arg Leu Ser Ser Met Val 115 120 125

Lys Lys Val Arg Leu Pro Ser Arg Cys Glu Pro Pro Gly Thr Thr Cys 130 135 140

Thr Val Ser Gly Trp Gly Thr Thr Thr Ser Pro Asp Val Thr Phe Pro 145 150 150 155 160

Ser Asp Leu Met Cys Val Asp Val Lys Leu Ile Ser Pro Gln Asp Cys 165 170 175

Thr Lys Val Tyr Lys Asp Leu Leu Glu Asn Ser Met Leu Cys Ala Gly 180 185 190

Ile Pro Asp Ser Lys Lys Asn Ala Cys Asn Gly Asp Ser Gly Gly Pro 195  $\phantom{\bigg|}$ 

Leu Val Cys Arg Gly Thr Leu Gln Gly Leu Val Ser Trp Gly Thr Phe 210 220

Pro Cys Gly Gln Pro Asn Asp Pro Gly Val Tyr Thr Gln Val Cys Lys 225 230 235 240

Phe Thr Lys Trp Ile Asn Asp Thr Met Lys Lys His Arg 245 250

<210> 182 <211> 169

<212> PRT

<213> Homo sapiens

<400> 182

Met Leu Ala Thr Arg Val Phe Ser Leu Val Gly Lys Arg Ala Ile Ser 1 5 10 15

Thr Ser Val Cys Val Arg Ala His Glu Ser Val Val Lys Ser Glu Asp  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Phe Ser Leu Pro Ala Tyr Met Asp Arg Arg Asp His Pro Leu Pro Glu 35 40 45

Val Ala His Val Lys His Leu Ser Ala Ser Gln Lys Ala Leu Lys Glu 50 60

Lys Glu Lys Ala Ser Trp Ser Ser Leu Ser Met Asp Glu Lys Val Glu 65 70 75 80

Leu Tyr Arg Ile Lys Phe Lys Glu Ser Phe Ala Glu Met Asn Arg Gly  $85 \hspace{0.5cm} 90 \hspace{0.5cm} 95$ 

Ser Asn Glu Trp Lys Thr Val Val Gly Gly Ala Met Phe Phe Ile Gly 100 105 110

Phe Thr Ala Leu Val Ile Met Trp Gln Lys His Tyr Val Tyr Gly Pro 115 125 125

Leu Pro Gln Ser Phe Asp Lys Glu Trp Val Ala Lys Gln Thr Lys Arg 130 135 140

Met Leu Asp Met Lys Val Asn Pro Ile Gln Gly Leu Ala Ser Lys Trp 145 150 155 160

Asp Tyr Glu Lys Asn Glu Trp Lys Lys 165

<210> 183

<211> 879 <212> PRT

<213> Homo sapiens

<400> 183

Met Ala Gly Gly Gly Asp Leu Ser Thr Arg Arg Leu Asn Glu Cys 1 5 10 15

Ile Ser Pro Val Ala Asn Glu Met Asn His Leu Pro Ala His Ser His 20 25 30

Asp Leu Gln Arg Met Phe Thr Glu Asp Gln Gly Val Asp Asp Arg Leu 35 40 45

Leu Tyr Asp Ile Val Phe Lys His Phe Lys Arg Asn Lys Val Glu Ile 50 60

Ser Asn Ala Ile Lys Lys Thr Phe Pro Phe Leu Glu Gly Leu Arg Asp 65 70 75 80

Arg Asp Leu Ile Thr Asn Lys Met Phe Glu Asp Ser Gln Asp Ser Cys 85 90 95

 Arg Asn Leu Val Pro Val Gln Arg Val Val Tyr Asn Val Leu Ser Glu 100

 Leu Glu Lys Thr Phe Asn Leu Pro Val Leu Glu Ala Leu Phe Ser Asp 115

Val Asn Met Gln Glu Tyr Pro Asp Leu Ile His Ile Tyr Lys Gly Phe 130 140

Glu Asn Val Ile His Asp Lys Leu Pro Leu Gln Glu Ser Glu Glu Glu 145 150 155 160

Glu Arg Glu Glu Arg Ser Gly Leu Gln Leu Ser Leu Glu Gln Gly Thr

Gly Glu Asn Ser Phe Arg Ser Leu Thr Trp Pro Pro Ser Gly Ser Pro 180 185 190

Ser His Ala Gly Thr Thr Pro Pro Glu Asn Gly Leu Ser Glu His Pro  $195 \hspace{1.5cm} 200 \hspace{1.5cm} 205 \hspace{1.5cm}$ 

Cys Glu Thr Glu Gln Ile Asn Ala Lys Arg Lys Asp Thr Thr Ser Asp 210 215 220

Lys Asp Asp Ser Leu Gly Ser Gln Gln Thr Asn Glu Gln Cys Ala Gln 225 230 235 240

Lys Ala Glu Pro Thr Glu Ser Cys Glu Gln Ile Ala Val Gln Val Asn  $245 \hspace{1.5cm} 255 \hspace{1.5cm}$ 

Asn Gly Asp Ala Gly Arg Glu Met Pro Cys Pro Leu Pro Cys Asp Glu 260 265 270

Glu Ser Pro Glu Ala Glu Leu His Asn His Gly Ile Gln Ile Asn Ser 275 280 285

Cys Ser Val Arg Leu Val Asp Ile Lys Lys Glu Lys Pro Phe Ser Asn 290 295 300

Ser Lys Val Glu Cys Gln Ala Gln Ala Arg Thr His His Asn Gln Ala 305  $\phantom{\bigg|}310\phantom{\bigg|}315\phantom{\bigg|}320\phantom{\bigg|}$ 

Ser Asp Ile Ile Val Ile Ser Ser Glu Asp Ser Glu Gly Ser Thr Asp 325 330 335

Val Asp Glu Pro Leu Glu Val Phe Ile Ser Ala Pro Arg Ser Glu Pro 340 345 350

Val Ile Asn Asn Asp Asn Pro Leu Glu Ser Asn Asp Glu Lys Glu Gly  $355 \hspace{1cm} 360 \hspace{1cm} 365$ 

Gln Glu Ala Thr Cys Ser Arg Pro Gln Ile Val Pro Glu Pro Met Asp 370 . 375 380

Phe Arg Lys Leu Ser Thr Phe Arg Glu Ser Phe Lys Lys Arg Val Ile 385 390 395 400

Gly Gln Asp His Asp Phe Ser Glu Ser Ser Glu Glu Glu Ala Pro Ala 415

Glu Ala Ser Ser Gly Ala Leu Arg Ser Lys His Gly Glu Lys Ala Pro  $420 \hspace{1cm} 425 \hspace{1cm} 430 \hspace{1cm}$ Met Thr Ser Arg Ser Thr Ser Thr Trp Arg Ile Pro Ser Arg Lys Arg 435 440 445 Arg Phe Ser Ser Ser Asp Phe Ser Asp Leu Ser Asn Gly Glu Glu Leu 450 455 460 Gln Glu Thr Cys Ser Ser Ser Leu Arg Arg Gly Ser Gly Ser Gln Pro 465 470 480 Gln Glu Pro Glu Asn Lys Lys Cys Ser Cys Val Met Cys Phe Pro Lys 485 490 495Gly Val Pro Arg Ser Gln Glu Ala Arg Thr Glu Ser Ser Gln Ala Ser 500 505 510Asp Met Met Asp Thr Met Asp Val Glu Asn Asn Ser Thr Leu Glu Lys 515 525His Ser Gly Lys Arg Arg Lys Lys Arg Arg His Arg Ser Lys Val Asn 530 540 Gly Leu Gln Arg Gly Arg Lys Lys Asp Arg Pro Arg Lys His Leu Thr 545 550 555 560 Leu Asn Asn Lys Val Gln Lys Lys Arg Trp Gln Gln Arg Gly Arg Lys 565 570 575 Ala Asn Thr Arg Pro Leu Lys Arg Arg Arg Lys Arg Gly Pro Arg Ile 580 585 590Pro Lys Asp Glu Asn Ile Asn Phe Lys Gln Ser Glu Leu Pro Val Thr 595 600 605 Cys Gly Glu Val Lys Gly Thr Leu Tyr Lys Glu Arg Phe Lys Gln Gly 610 620Thr Ser Lys Lys Cys Ile Gln Ser Glu Asp Lys Lys Trp Phe Thr Pro 625 630 635 640 Arg Glu Phe Glu Ile Glu Gly Asp Arg Gly Ala Ser Lys Asn Trp Lys 645 650 655Leu Ser Ile Arg Cys Gly Gly Tyr Thr Leu Lys Val Leu Met Glu Asn 660 665 670 Lys Phe Leu Pro Glu Pro Pro Ser Thr Arg Lys Lys Arg Ile Leu Glu 675 680 685 Ser His Asn Asn Thr Leu Val Asp Pro Cys Glu Glu His Lys Lys 690 695 700 Asn Pro Asp Ala Ser Val Lys Phe Ser Glu Phe Leu Lys Lys Cys Ser 705 710 715 720 Glu Thr Trp Lys Thr Ile Phe Ala Lys Glu Lys Gly Lys Phe Glu Asp Page 288

725 730 735

Met Ala Lys Ala Asp Lys Ala His Tyr Glu Arg Glu Met Lys Thr Tyr 740 745 750

The Pro Pro Lys Gly Glu Lys Lys Lys Lys Phe Lys Asp Pro Asn Ala 755 760 765

Pro Lys Arg Pro Pro Leu Ala Phe Phe Leu Phe Cys Ser Glu Tyr Arg 770 780

Pro Lys Ile Lys Gly Glu His Pro Gly Leu Ser Ile Asp Asp Val Val 785 790 795 800

Lys Lys Leu Ala Gly Met Trp Asn Asn Thr Ala Ala Ala Asp Lys Gln 805 810 815

Phe Tyr Glu Lys Lys Ala Ala Lys Leu Lys Glu Lys Tyr Lys Lys Asp 820 825 830

Ile Ala Ala Tyr Arg Ala Lys Gly Lys Pro Asn Ser Ala Lys Lys Arg 835 840 845

Val Val Lys Ala Glu Lys Ser Lys Lys Lys Lys Glu Glu Glu Glu Asp 850 855 860

Glu Glu Asp Glu Glu Glu Glu Glu Asn Glu Glu Asp Asp Asp Lys 865 870 875

<210> 184

<211> 316

<212> PRT

<213> Homo sapiens

<400> 184

Asn His Pro Asp Ala Ile Leu Val Glu Asp Tyr Arg Ala Gly Asp Met 20 25 30

Ile Cys Pro Glu Cys Gly Leu Val Val Gly Asp Arg Val Ile Asp Val 35 40 45

Gly Ser Glu Trp Arg Thr Phe Ser Asn Asp Lys Ala Thr Lys Asp Pro 50 60

Ser Arg Val Gly Asp Ser Gln Asn Pro Leu Leu Ser Asp Gly Asp Leu 65 70 75 80

Ser Thr Met Ile Gly Lys Gly Thr Gly Ala Ala Ser Phe Asp Glu Phe  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Gly Asn Ser Lys Tyr Gln Asn Arg Arg Thr Met Ser Ser Ser Asp Arg

Ala Met Met Asn Ala Phe Lys Glu Ile Thr Thr Met Ala Asp Arg Ile 115 120 125

Asn Leu Pro Arg Asn Ile Val Asp Arg Thr Asn Asn Leu Phe Lys Gln

130 135 14

Val Tyr Glu Gln Lys Ser Leu Lys Gly Arg Ala Asn Asp Ala Ile Ala 145 150 155 160

Ser Ala Cys Leu Tyr Ile Ala Cys Arg Gln Glu Gly Val Pro Arg Thr 165 170 175

Phe Lys Glu Ile Cys Ala Val Ser Arg Ile Ser Lys Lys Glu Ile Gly 180 185 190

Arg Cys Phe Lys Leu Ile Leu Lys Ala Leu Glu Thr Ser Val Asp Leu 195 200 205

Ile Thr Thr Gly Asp Phe Met Ser Arg Phe Cys Ser Asn Leu Cys Leu 210 215 220

Pro Lys Gln Val Gln Met Ala Ala Thr His Ile Ala Arg Lys Ala Val 225 230 235 240

Glu Leu Asp Leu Val Pro Gly Arg Ser Pro Ile Ser Val Ala Ala Ala 245 250 255

Ala Ile Tyr Met Ala Ser Gln Ala Ser Ala Glu Lys Arg Thr Gln Lys 260 265 270

Glu Ile Gly Asp Ile Ala Gly Val Ala Asp Val Thr Ile Arg Gln Ser  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285$ 

Tyr Arg Leu Ile Tyr Pro Arg Ala Pro Asp Leu Phe Pro Thr Asp Phe 290 295 300

Lys Phe Asp Thr Pro Val Asp Lys Leu Pro Gln Leu 305 310 315

<210> 185

211> 628

<212> PRT

<213> Homo sapiens

<400> 185

Ala Asp Phe Leu Asp Ala Leu Ile Val Ser Met Asp Val Ile Gln His 1  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Glu Thr Ile Gly Lys Lys Phe Glu Lys Arg His Ile Glu Ile Phe Thr 20 25 30

Asp Leu Ser Ser Arg Phe Ser Lys Ser Gln Leu Asp Ile Ile Ile His  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45 \hspace{1.5cm}$ 

Ser Leu Lys Lys Cys Asp Ile Ser Leu Gln Phe Phe Leu Pro Phe Ser 50 60

Leu Gly Lys Glu Asp Gly Ser Gly Asp Arg Gly Asp Gly Pro Phe Arg 65 70 75 80

Leu Gly Gly His Gly Pro Ser Phe Pro Leu Lys Gly Ile Thr Glu Gln  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Gln Lys Glu Gly Leu Glu Ile Val Lys Met Val Met Ile Ser Leu Glu

100 105 110

Gly Glu Asp Gly Leu Asp Glu Ile Tyr Ser Phe Ser Glu Ser Leu Arg 125

Lys Leu Cys Val Phe Lys Lys Ile Glu Arg His Ser Ile His Trp Pro 130

Cys Arg Leu Thr Ile Gly Ser Asn Leu Ser Ile Arg Ile Ala Ala Tyr 145

Lys Ser Ile Leu Gln Glu Arg Val Lys Lys Thr Trp Thr Val Val Asp 165 . . 170 175

Ala Lys Thr Leu Lys Lys Glu Asp Ile Gln Lys Glu Thr Val Tyr Cys 180 185 190

Leu Asn Asp Asp Asp Glu Thr Glu Val Leu Lys Glu Asp Ile Ile Gln 195 200 205

Gly Phe Leu Tyr Gly Ser Asp Ile Val Pro Phe Ser Lys Val Asp Glu 210 215 220

Glu Gln Met Lys Tyr Lys Ser Glu Gly Lys Cys Phe Ser Val Leu Gly 225 230 235 240

Phe Cys Lys Ser Ser Gln Val Gln Arg Arg Phe Phe Met Gly Asn Gln 245 250 255

Val Leu Lys Val Phe Ala Ala Arg Asp Asp Glu Ala Ala Ala Val Ala 260 265 270

Leu Ser Ser Leu Ile His Ala Leu Asp Asp Leu Asp Met Val Ala Ile 275 280 285

Val Arg Tyr Ala Tyr Asp Lys Arg Ala Asn Pro Gln Val Gly Val Ala 290 295 300

Phe Pro His Ile Lys His Asn Tyr Glu Cys Leu Val Tyr Val Gln Leu 305 310 315 320

Pro Phe Met Glu Asp Leu Arg Gln Tyr Met Phe Ser Ser Leu Lys Asn 325 330 335

Ser Lys Lys Tyr Ala Pro Thr Glu Ala Gln Leu Asn Ala Val Asp Ala 340 345 350

Leu Ile Asp Ser Met Ser Leu Ala Lys Lys Asp Glu Lys Thr Asp Thr 355 360 365

Leu Glu Asp Leu Phe Pro Thr Thr Lys Ile Pro Asn Pro Arg Phe Gln 370 375 380

Arg Leu Phe Gln Cys Leu Leu His Arg Ala Leu His Pro Arg Glu Pro 385 390 395 400

Leu Pro Pro Ile Gln Gln His Ile Trp Asn Met Leu Asn Pro Pro Ala 405 410 415

Glu Val Thr Thr Lys Ser Gln Ile Pro Leu Ser Lys Ile Lys Thr Leu  $420 \hspace{1.5cm} 425 \hspace{1.5cm} 430$ 

Phe Pro Leu Ile Glu Ala Lys Lys Lys Asp Gln Val Thr Ala Gln Glu 435  $\phantom{\bigg|}440\phantom{\bigg|}$ 

Ile Phe Gln Asp Asn His Glu Asp Gly Pro Thr Ala Lys Lys Leu Lys 450 455 460

Thr Glu Gln Gly Gly Ala His Phe Ser Val Ser Ser Leu Ala Glu Gly 465 470 475 480

Ser Val Thr Ser Val Gly Ser Val Asn Pro Ala Glu Asn Phe Arg Val 485 490 495

Leu Val Lys Gln Lys Lys Ala Ser Phe Glu Glu Ala Ser Asn Gln Leu 500 505 510

Ile Asn His Ile Glu Gln Phe Leu Asp Thr Asn Glu Thr Pro Tyr Phe 515 520 525

Met Lys Ser Ile Asp Cys Ile Arg Ala Phe Arg Glu Glu Ala Ile Lys 530 535 540

Phe Ser Glu Glu Gln Arg Phe Asn Asn Phe Leu Lys Ala Leu Gln Glu 545 550 560

Lys Val Glu Ile Lys Gln Leu Asn His Phe Trp Glu Ile Val Val Gln 565  $\phantom{0}570$   $\phantom{0}575$ 

Thr Ala Glu Glu Ala Lys Lys Phe Leu Ala Pro Lys Asp Lys Pro Ser  $595 \hspace{1.5cm} 600 \hspace{1.5cm} 605$ 

Gly Asp Thr Ala Ala Val Phe Glu Glu Gly Gly Asp Val Asp Asp Leu 610 620

Leu Asp Met Ile

<210> 186

<211> 420 <212> PRT

<213> Homo sapiens

<400> 186

Met Gly Ser Gly Trp Lys Lys Ile Lys Leu Gln Met Lys Cys Asp Gly 1 5 10 15

Cys Ser Glu Gln Gly Ser His Pro Cys Ala Phe Ile Gly Ile Gly Asn 20 25 30

Ser Asp Gln Glu Met Gln Gln Leu Asn Leu Glu Gly Lys Asn Tyr Cys  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Thr Ala Lys Thr Leu Tyr Ile Ser Asp Ser Asp Lys Gln Lys His Phe 50 60

Met Leu Ser Val Lys Val Phe Tyr Gly Asn Gly Asp Asp Ile Gly Val 65 70 75 80

Phe Leu Ser Lys Ser Ser Lys Pro Ser Lys Lys Lys Gln Ser Leu Lys 85 90 95

Asn Ala Asp Leu Cys Ile Gly Ser Gly Thr Lys Val Ala Leu Phe Asn 100 105 110

Arg Leu Arg Ser Gln Thr Val Ser Thr Arg Tyr Leu His Val Glu Gly 115 120 125

Gly Asn Phe His Ala Ser Ser Gln Gln Trp Gly Ala Phe Thr Leu Phe 130 135 140

Leu Asp Asp Asp Gly Ser Glu Gly Glu Glu Phe Thr Val Arg Asp Gly 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}160\phantom{\bigg|}$ 

Tyr Ile His Tyr Gly Gln Thr Val Lys Leu Val Cys Ser Val Thr Gly 165 170 175

Met Ala Leu Pro Arg Leu Ile Ile Arg Lys Val Asp Lys Gln Thr Thr 180 185 190

Leu Leu Asp Ala Asp Asp Pro Val Ser Gln Leu His Lys Cys Ala Phe 195 200 205

Asp Leu Glu Asp Thr Glu Arg Met Tyr Leu Cys Leu Ser Gln Glu Arg  $210 \hspace{1.5cm} 215 \hspace{1.5cm} 220 \hspace{1.5cm}$ 

Ile Ile Gln Phe Gln Ala Thr Pro Cys Pro Thr Glu Pro Asn Lys Glu 225 230 230 235

Met Ile Asn Asp Gly Ala Ser Trp Ala Ile Ile Ser Thr His Lys Ala 245 250 255

Lys Tyr Thr Phe Tyr Glu Arg Met Gly Pro Val Leu Ala Leu Val Met 260 265 270

Pro Met Pro Val Val Glu Ser Leu Lys Leu Asn Gly Gly Gly Asp Glu 275 280 285

Ala Met Leu Glu Leu Thr Gly Gln Asn Phe Thr Pro Asn Leu Arg Val 290 300

Trp Phe Gly Asp Val Glu Ala Glu Thr Met Tyr Arg Cys Gly Glu Ser 305 310 315 320

Met Leu Arg Val Val Pro Asp Val Leu His Ser Glu Lys Val Gly Asp 325 330 335

Ser Ser Gln Gln Pro Val Gln Val Ser Val Thr Leu Val Arg Asn Asp 340 345 350

Gly Ile Ile Tyr Ser Thr Ser Leu Thr Phe Thr Tyr Thr Pro Glu Ala 355 360 365

Gly Pro Arg Pro His Cys Ser Val Ala Gly Ala Ile Leu Lys Ala Ser 370 380

Ser Ser His Val Pro Pro Asn Glu Leu Asn Thr Asn Ser Asp Gly Ser 385 390 395 400

Tyr Thr Asn Ala Ser Thr Asn Ser Thr Ser Val Thr Ser Ser Thr Pro 405  $\phantom{000}$  410  $\phantom{000}$  415

Thr Val Val Ser 420

<210> 187

<211> 10

<212> PRT

<213> Homo sapiens

<400> 187

Met Glu Thr Val Glu Leu Ile Pro Leu Ala Lys Glu Met Met Ala 1 5 10 15

Gln Lys Arg Lys Gly Lys Met Val Lys Leu Tyr Val Leu Gly Ser Val 20 25 30

Leu Ala Leu Phe Gly Val Val Leu Gly Leu Met Glu Thr Val Cys Ser 35 40 45

Pro Phe Thr Ala Ala Arg Arg Leu Arg Asp Gln Glu Ala Ala Val Ala 50 55 60

Glu Leu Gln Ala Ala Leu Glu Arg Gln Ala Leu Gln Lys Gln Ala Leu 65 70 75 80

Gln Glu Lys Gly Lys Gln Gln Asp Thr Val Leu Gly Gly Arg Ala Leu 85 90 95

Ser Asn Arg Gln His Ala Ser 100

<210> 188

<211> 1306

<212> PRT

<213> Homo sapiens

<400> 188

Met Gly Ala Ala Ser Gly Arg Arg Gly Pro Gly Leu Leu Pro Leu 1 5 10 15

Pro Leu Leu Leu Leu Pro Pro Gln Pro Ala Leu Ala Leu Asp Pro 20 25 30

Gly Leu Gln Pro Gly Asn Phe Ser Ala Asp Glu Ala Gly Ala Gln Leu  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Phe Ala Gln Ser Tyr Asn Ser Ser Ala Glu Gln Val Leu Phe Gln Ser 50 60

Val Ala Ala Ser Trp Ala His Asp Thr Asn Ile Thr Ala Glu Asn Ala 65 70 75 80

Arg Arg Gln Glu Glu Ala Ala Leu Leu Ser Gln Glu Phe Ala Glu Ala 85 90 95

Trp Gly Gln Lys Ala Lys Glu Leu Tyr Glu Pro Ile Trp Gln Asn Phe  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110$ 

Thr Asp Pro Gln Leu Arg Arg Ile Ile Gly Ala Val Arg Thr Leu Gly 115 120 125

Ser Ala Asn Leu Pro Leu Ala Lys Arg Gln Gln Tyr Asn Ala Leu Leu 130 135 140

Ser Asn Met Ser Arg Ile Tyr Ser Thr Ala Lys Val Cys Leu Pro Asn 145 150 155 160

Lys Thr Ala Thr Cys Trp Ser Leu Asp Pro Asp Leu Thr Asn Ile Leu 165 170 175

Ala Ser Ser Arg Ser Tyr Ala Met Leu Leu Phe Ala Trp Glu Gly Trp 180 185 190

His Asn Ala Ala Gly Ile Pro Leu Lys Pro Leu Tyr Glu Asp Phe Thr

Ala Leu Ser Asn Glu Ala Tyr Lys Gln Asp Gly Phe Thr Asp Thr Gly 210 215 220

Ala Tyr Trp Arg Ser Trp Tyr Asn Ser Pro Thr Phe Glu Asp Asp Leu 225 230 230 235

Glu His Leu Tyr Gln Gln Leu Glu Pro Leu Tyr Leu Asn Leu His Ala 245 250 250 255

Phe Val Arg Arg Ala Leu His Arg Arg Tyr Gly Asp Arg Tyr Ile Asn 260 265 270

Ser Trp Glu Asn Ile Tyr Asp Met Val Val Pro Phe Pro Asp Lys Pro 290 300

Asn Leu Asp Val Thr Ser Thr Met Leu Gln Gln Gly Trp Asn Ala Thr 305 310 315 320

His Met Phe Arg Val Ala Glu Glu Phe Phe Thr Ser Leu Glu Leu Ser 325 335

Pro Met Pro Pro Glu Phe Trp Glu Gly Ser Met Leu Glu Lys Pro Ala 340 345 350

Asp Gly Arg Glu Val Val Cys His Ala Ser Ala Trp Asp Phe Tyr Asn 355 360 365

Arg Lys Asp Phe Arg Ile Lys Gln Cys Thr Arg Val Thr Met Asp Gln 370 380

Leu Ser Thr Val His His Glu Met Gly His Ile Gln Tyr Tyr Leu Gln 385 390 395 400

Tyr Lys Asp Leu Pro Val Ser Leu Arg Arg Gly Ala Asn Pro Gly Phe 405 410 415

His Glu Ala Ile Gly Asp Val Leu Ala Leu Ser Val Ser Thr Pro Glu 420 425 430

His Leu His Lys Ile Gly Leu Leu Asp Arg Val Thr Asn Asp Thr Glu 435 440 445

Leu Pro Phe Gly Tyr Leu Val Asp Gln Trp Arg Trp Gly Val Phe Ser 465 470 475 480

Gly Arg Thr Pro Pro Ser Arg Tyr Asn Phe Asp Trp Trp Tyr Leu Arg 485 490 495

Thr Lys Tyr Gln Gly Ile Cys Pro Pro Val Thr Arg Asn Glu Thr His  $500 \hspace{1.5cm} 505 \hspace{1.5cm} 510$ 

Phe Asp Ala Gly Ala Lys Phe His Val Pro Asn Val Thr Pro Tyr Ile 515 520 525

Arg Tyr Phe Val Ser Phe Val Leu Gln Phe Gln Phe His Glu Ala Leu 530 540

Cys Lys Glu Ala Gly Tyr Glu Gly Pro Leu His Gln Cys Asp Ile Tyr 545 550 555 560

Arg Ser Thr Lys Ala Gly Ala Lys Leu Arg Lys Val Leu Gln Ala Gly 565 570 575

Ser Ser Arg Pro Trp Gln Glu Val Leu Lys Asp Met Val Gly Leu Asp 580 595 595

Ala Leu Asp Ala Gln Pro Leu Leu Lys Tyr Phe Gln Pro Val Thr Gln 595 605 605

Trp Leu Gln Glu Gln Asn Gln Gln Asn Gly Glu Val Leu Gly Trp Pro 610 615 620

Glu Tyr Gln Trp His Pro Pro Leu Pro Asp Asn Tyr Pro Glu Gly Ile 625 630 635 640

Asp Leu Val Thr Asp Glu Ala Glu Ala Ser Lys Phe Val Glu Glu Tyr  $645 \hspace{1cm} 650 \hspace{1cm} 655$ 

Asp Arg Thr Ser Gln Val Val Trp Asn Glu Tyr Ala Glu Ala Asn Trp 660 665 670

Asn Tyr Asn Thr Asn Ile Thr Thr Glu Thr Ser Lys Ile Leu Leu Gln 675 680 685

Lys Asn Met Gln Ile Ala Asn His Thr Leu Lys Tyr Gly Thr Gln Ala 690 695 700

Arg Lys Phe Asp Val Asn Gln Leu Gln Asn Thr Thr Ile Lys Arg Ile 705 710 715 720

Ile Lys Lys Val Gln Asp Leu Glu Arg Ala Ala Leu Pro Ala Gln Glu 725 730 735

Leu Glu Glu Tyr Asn Lys Ile Leu Leu Asp Met Glu Thr Thr Tyr Ser 740 745 750

Val Ala Thr Val Cys His Pro Asn Gly Ser Cys Leu Gln Leu Glu Pro  $755 \hspace{1.5cm} 760 \hspace{1.5cm} 765$ 

Asp Leu Thr Asn Val Met Ala Thr Ser Arg Lys Tyr Glu Asp Leu Leu 770 780

Trp Ala Trp Glu Gly Trp Arg Asp Lys Ala Gly Arg Ala Ile Leu Gln 785 790 795 800

Phe Tyr Pro Lys Tyr Val Glu Leu Ile Asn Gln Ala Ala Arg Leu Asn 815

Ser Leu Glu Gln Asp Leu Glu Arg Leu Phe Gln Glu Leu Gln Pro Leu 835 840 845

Tyr Leu Asn Leu His Ala Tyr Val Arg Arg Ala Leu His Arg His Tyr 850 855 860

Gly Ala Gln His Ile Asn Leu Glu Gly Pro Ile Pro Ala His Leu Leu 865 870 875 880

Gly Asn Met Trp Ala Gln Thr Trp Ser Asn Ile Tyr Asp Leu Val Val 885 890 895

Pro Phe Pro Ser Ala Pro Ser Met Asp Thr Thr Glu Ala Met Leu Lys 900 905 910

Gln Gly Trp Thr Pro Arg Arg Met Phe Lys Glu Ala Asp Asp Phe Phe 915 920 925

Thr Ser Leu Gly Leu Leu Pro Val Pro Pro Glu Phe Trp Asn Lys Ser 930 935 940

Met Leu Glu Lys Pro Thr Asp Gly Arg Glu Val Val Cys His Ala Ser 945 950 955 960

Ala Trp Asp Phe Tyr Asn Gly Lys Asp Phe Arg Ile Lys Gln Cys Thr 965 970 975

Thr Val Asn Leu Glu Asp Leu Val Val Ala His His Glu Met Gly His  $980 \hspace{1.5cm} 985 \hspace{1.5cm} 990$ 

Ile Gln Tyr Phe Met Gln Tyr Lys Asp Leu Pro Val Ala Leu Arg Glu 995 1000 1005

Gly Ala Asn Pro Gly Phe His Glu Ala Ile Gly Asp Val Leu Ala 1010 1020

Leu Ser Val Ser Thr Pro Lys His Leu His Ser Leu Asn Leu Leu 1025 1030 1035

Ser Ser Glu Gly Gly Ser Asp Glu His Asp Ile Asn Phe Leu Met Page 297

1040 1045 1050

Lys Met Ala Leu Asp Lys Ile Ala Phe Ile Pro Phe Ser Tyr Leu 1055 1060 1065

Val Asp Gln Trp Arg Trp Arg Val Phe Asp Gly Ser Ile Thr Lys 1070 1075 1080

Glu Asn Tyr Asn Gln Glu Trp Trp Ser Leu Arg Leu Lys Tyr Gln 1085 1090 1095

Gly Leu Cys Pro Pro Val Pro Arg Thr Gln Gly Asp Phe Asp Pro 1100 1105 1110

Gly Ala Lys Phe His Ile Pro Ser Ser Val Pro Tyr Ile Arg Tyr 1115 1120 1125

Phe Val Ser Phe Ile Ile Gln Phe Gln Phe His Glu Ala Leu Cys 1130 1140

Gln Ala Ala Gly His Thr Gly Pro Leu His Lys Cys Asp Ile Tyr 1145 1150 1155

Gln Ser Lys Glu Ala Gly Gln Arg Leu Ala Thr Ala Met Lys Leu 1160 1165 1170

Gly Phe Ser Arg Pro Trp Pro Glu Ala Met Gln Leu Ile Thr Gly 1175 1180 1185

Gln Pro Asn Met Ser Ala Ser Ala Met Leu Ser Tyr Phe Lys Pro 1190 1195 1200

Leu Leu Asp Trp Leu Arg Thr Glu Asn Glu Leu His Gly Glu Lys 1205 1210 1215

Leu Gly Trp Pro Gln Tyr Asn Trp Thr Pro Asn Ser Ala Arg Ser 1220 1225

Glu Gly Pro Leu Pro Asp Ser Gly Arg Val Ser Phe Leu Gly Leu 1235 1240 1245

Asp Leu Asp Ala Gln Gln Ala Arg Val Gly Gln Trp Leu Leu Leu 1250 1260

Phe Leu Gly Ile Ala Leu Leu Val Ala Thr Leu Gly Leu Ser Gln 1265 . 1270 1275

Arg Leu Phe Ser Ile Arg His Arg Ser Leu His Arg His Ser His 1280 1285 1290

Gly Pro Gln Phe Gly Ser Glu Val Glu Leu Arg His Ser 1295 1300 1305

<210> 189 <211> 1461

<212> PRT

<213> Homo sapiens

<400> 189

Met Ala Ala Glu Arg Gly Ala Arg Arg Leu Leu Ser Thr Pro Ser Phe

1 5 10 15

Trp Leu Tyr Cys Leu Leu Leu Gly Arg Arg Ala Pro Gly Ala Ala 20 25 30

Ala Ala Arg Ser Gly Ser Ala Pro Gln Ser Pro Gly Ala Ser Ile Arg  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Thr Phe Thr Pro Phe Tyr Phe Leu Val Glu Pro Val Asp Thr Leu Ser 50

Val Arg Gly Ser Ser Val Ile Leu Asn Cys Ser Ala Tyr Ser Glu Pro 65 70 75 80

Ser Pro Lys Ile Glu Trp Lys Lys Asp Gly Thr Phe Leu Asn Leu Val

Ser Asp Asp Arg Gln Leu Leu Pro Asp Gly Ser Leu Phe Ile Ser 100 105 110

Asn Val Val His Ser Lys His Asn Lys Pro Asp Glu Gly Tyr Tyr Gln 115 120 125

Cys Val Ala Thr Val Glu Ser Leu Gly Thr Ile Ile Ser Arg Thr Ala 130  $$135\$ 

Lys Leu Ile Val Ala Gly Leu Pro Arg Phe Thr Ser Gln Pro Glu Pro 145  $\phantom{\bigg|}$  150  $\phantom{\bigg|}$  155  $\phantom{\bigg|}$  160

Ser, Ser Val Tyr Ala Gly Asn Gly Ala Ile Leu Asn Cys Glu Val Asn 165 170 175

Ala Asp Leu Val Pro Phe Val Arg Trp Glu Gln Asn Arg Gln Pro Leu 180 185 190

Leu Leu Asp Asp Arg Val Ile Lys Leu Pro Ser Gly Met Leu Val Ile 195 200 205

Ser Asn Ala Thr Glu Gly Asp Gly Gly Leu Tyr Arg Cys Val Val Glu 210 215 220

Ser Gly Gly Pro Pro Lys Tyr Ser Asp Glu Val Glu Leu Lys Val Leu 225 230 235

Pro Asp Pro Glu Val Ile Ser Asp Leu Val Phe Leu Lys Gln Pro Ser 245  $\phantom{\bigg|}250\phantom{\bigg|}$ 

Pro Leu Val Arg Val Ile Gly Gln Asp Val Val Leu Pro Cys Val Ala 260 265 270

Ser Gly Leu Pro Thr Pro Thr Ile Lys Trp Met Lys Asn Glu Glu Ala 275  $\phantom{\bigg|}280\phantom{\bigg|}285\phantom{\bigg|}$ 

Leu Asp Thr Glu Ser Ser Glu Arg Leu Val Leu Leu Ala Gly Gly Ser 290 295 300

Leu Glu Ile Ser Asp Val Thr Glu Asp Asp Ala Gly Thr Tyr Phe Cys 305 310 315 320

Ile Ala Asp Asn Gly Asn Glu Thr Ile Glu Ala Gln Ala Glu Leu Thr 325 330 335

Val Gln Ala Gln Pro Glu Phe Leu Lys Gln Pro Thr Asn Ile Tyr Ala 340 345 350

His Glu Ser Met Asp Ile Val Phe Glu Cys Glu Val Thr Gly Lys Pro  $355 \hspace{1.5cm} 360 \hspace{1.5cm} 365$ 

Thr Pro Thr Val Lys Trp Val Lys Asn Gly Asp Met Val Ile Pro Ser 370 380

Asp Tyr Phe Lys Ile Val Lys Glu His Asn Leu Gln Val Leu Gly Leu 385 390 395 400

Val Lys Ser Asp Glu Gly Phe Tyr Gln Cys Ile Ala Glu Asn Asp Val 405 410 415

Gly Asn Ala Gln Ala Gly Ala Gln Leu Ile Ile Leu Glu His Ala Pro  $420 \hspace{1.5cm} 425 \hspace{1.5cm} 430$ 

Ala Thr Thr Gly Pro Leu Pro Ser Ala Pro Arg Asp Val Val Ala Ser  $435 \ \ \, 440 \ \ \, 445$ 

Leu Val Ser Thr Arg Phe Ile Lys Leu Thr Trp Arg Thr Pro Ala Ser 450 455 460

Asp Pro His Gly Asp Asn Leu Thr Tyr Ser Val Phe Tyr Thr Lys Glu 465 470 475 480

Gly Ile Ala Arg Glu Arg Val Glu Asn Thr Ser His Pro Gly Glu Met 485 490 495

Gln Val Thr Ile Gln Asn Leu Met Pro Ala Thr Val Tyr Ile Phe Arg 500 505 510

Val Met Ala Gln Asn Lys His Gly Ser Gly Glu Ser Ser Ala Pro Leu 515 520 525

Arg Val Glu Thr Gln Pro Glu Val Gln Leu Pro Gly Pro Ala Pro Asn 530 535 540

Leu Arg Ala Tyr Ala Ala Ser Pro Thr Ser Ile Thr Val Thr Trp Glu 545 550 555 560

Thr Pro Val Ser Gly Asn Gly Glu Ile Gln Asn Tyr Lys Leu Tyr Tyr 565 570 575

Met Glu Lys Gly Thr Asp Lys Glu Gln Asp Val Asp Val Ser Ser His 580 585 590

Ser Tyr Thr Ile Asn Gly Leu Lys Lys Tyr Thr Glu Tyr Ser Phe Arg  $595 \hspace{1.5cm} 600 \hspace{1.5cm} 605$ 

Val Val Ala Tyr Asn Lys His Gly Pro Gly Val Ser Thr Pro Asp Val 610 620

Ala Val Arg Thr Leu Ser Asp Val Pro Ser Ala Ala Pro Gln Asn Leu 625 630 635 640

Ser Leu Glu Val Arg Asn Ser Lys Ser Ile Met Ile His Trp Gln Pro 645 650 655

Pro Ala Pro Ala Thr Gln Asn Gly Gln Ile Thr Gly Tyr Lys Ile Arg
660 665 670

Tyr Arg Lys Ala Ser Arg Lys Ser Asp Val Thr Glu Thr Leu Val Ser 675 680 685

Gly Thr Gln Leu Ser Gln Leu Ile Glu Gly Leu Asp Arg Gly Thr Glu 690 695 700

Tyr Asn Phe Arg Val Ala Ala Leu Thr Ile Asn Gly Thr Gly Pro Ala 705 710 715 720

Thr Asp Trp Leu Ser Ala Glu Thr Phe Glu Ser Asp Leu Asp Glu Thr 725 730 730 735

Arg Val Pro Glu Val Pro Ser Ser Leu His Val Arg Pro Leu Val Thr  $740 \hspace{1.5cm} 745 \hspace{1.5cm} 750$ 

Ser Ile Val Val Ser Trp Thr Pro Pro Glu Asn Gln Asn Ile Val Val 755  $\phantom{\bigg|}$  760  $\phantom{\bigg|}$  765

Arg Gly Tyr Ala Ile Gly Tyr Gly Ile Gly Ser Pro His Ala Gln Thr 770 . 780

Ile Lys Val Asp Tyr Lys Gln Arg Tyr Tyr Thr Ile Glu Asn Leu Asp 785 790 795 800

Pro Ser Ser His Tyr Val Ile Thr Leu Lys Ala Phe Asn Asn Val Gly 805 810 810

Glu Gly Ile Pro Leu Tyr Glu Ser Ala Val Thr Arg Pro His Thr Asp 820 825 830

Thr Ser Glu Val Asp Leu Phe Val Ile Asn Ala Pro Tyr Thr Pro Val 835  $\phantom{\bigg|}840\phantom{\bigg|}$ 

Leu Ser His Asp Thr Ile Arg Ile Thr Trp Ala Asp Asn Ser Leu Pro 865 870 875 880

Lys His Gln Lys Ile Thr Asp Ser Arg Tyr Tyr Thr Val Arg Trp Lys 885 890 895

Thr Asn Ile Pro Ala Asn Thr Lys Tyr Lys Asn Ala Asn Ala Thr Thr  $900 \hspace{1.5cm} 905 \hspace{1.5cm} 910$ 

Leu Ser Tyr Leu Val Thr Gly Leu Lys Pro Asn Thr Leu Tyr Glu Phe 915 920 925

Ser Val Met Val Thr Lys Gly Arg Arg Ser Ser Thr Trp Ser Met Thr 930 940

Ala His Gly Thr Thr Phe Glu Leu Val Pro Thr Ser Pro Pro Lys Asp 945 950 950 960

Val Thr Val Val Ser Lys Glu Gly Lys Pro Lys Thr Ile Ile Val Asn 965 970 975

Trp Gln Pro Ser Glu Ala Asn Gly Lys Ile Thr Gly Tyr Ile Ile 980 985 990

Tyr Tyr Ser Thr Asp Val Asn Ala Glu Ile His Asp Trp Val Ile Glu 995 1000 1005

Pro Val Val Gly Asn Arg Leu Thr His Gln Ile Gln Glu Leu Thr 1010 1020

Leu Asp Thr Pro Tyr Tyr Phe Lys Ile Gln Ala Arg Asn Ser Lys 1025 1035

Gly Met Gly Pro Met Ser Glu Ala Val Gln Phe Arg Thr Pro Lys  $1040 \hspace{1.5cm} 1045 \hspace{1.5cm} 1050$ 

Ala Asp Ser Ser Asp Lys Met Pro Asn Asp Gln Ala Ser Gly Ser 1055 1060 1065

Pro Pro Met Ser Gly Ser Asn Ser Pro His Gly Ser Pro Thr Ser 1085 1090 1095

Pro Leu Asp Ser Asn Met Leu Leu Val Ile Ile Val Ser Val Gly 1100 1105 1110

Val Ile Thr Ile Val Val Val Val Ile Ile Ala Val Phe Cys Thr 1115 1120 1125

Arg Arg Thr Thr Ser His Gln Lys Lys Lys Arg Ala Ala Cys Lys 1130 1135 1140

Ser Val Asn Gly Ser His Lys Tyr Lys Gly Asn Ser Lys Asp Val 1145 1150 1155

Lys Pro Pro Asp Leu Trp Ile His His Glu Arg Leu Glu Leu Lys 1160  $$1165\ \ \ \ \, 1170\ \ \ \,$ 

Pro Ile Asp Lys Ser Pro Asp Pro Asn Pro Ile Met Thr Asp Thr 1175 1180 Pro Ile Met Thr Asp Thr

Pro Ile Pro Arg Asn Ser Gln Asp Ile Thr Pro Val Asp Asn Ser 1190 1195 1200

Met Asp Ser Asn Ile His Gln Arg Arg Asn Ser Tyr Arg Gly His 1205 1210 1215

Glu Ser Glu Asp Ser Met Ser Thr Leu Ala Gly Arg Arg Gly Met 1220 1230

Arg Pro Lys Met Met Met Pro Phe Asp Ser Gln Pro Pro Gln Pro 1235 1240

Val Ile Ser Ala His Pro Ile His Ser Leu Asp Asn Pro His His Page 302

1250 1255

His Phe His Ser Ser Ser Leu Ala Ser Pro Ala Arg Ser His Leu 1265 1270 1275

Tyr His Pro Gly Ser Pro Trp Pro Ile Gly Thr Ser Met Ser Leu 1280 1285 1290

Ser Asp Arg Ala Asn Ser Thr Glu Ser Val Arg Asn Thr Pro Ser 1295  $\phantom{\bigg|}$  1300  $\phantom{\bigg|}$  1305

Thr Asp Thr Met Pro Ala Ser Ser Ser Gln Thr Cys Cys Thr Asp 1310 - - 1315 1320

His Gln Asp Pro Glu Gly Ala Thr Ser Ser Ser Tyr Leu Ala Ser 1325 1330 1335

Ser Gln Glu Glu Asp Ser Gly Gln Ser Leu Pro Thr Ala His Val 1340 1345 1350

Arg Pro Ser His Pro Leu Lys Ser Phe Ala Val Pro Ala Ile Pro 1355 1360 1365

Pro Pro Gly Pro Pro Thr Tyr Asp Pro Ala Leu Pro Ser Thr Pro 1370 1375 1380

Leu Leu Ser Gln Gln Ala Leu Asn His His Ile His Ser Val Lys 1390

Thr Ala Ser Ile Gly Thr Leu Gly Arg Ser Arg Pro Pro Met Pro 1400 1405 1410

Val Val Val Pro Ser Ala Pro Glu Val Gln Glu Thr Thr Arg Met 1415 1420 1425

Leu Glu Asp Ser Glu Ser Ser Tyr Glu Pro Asp Glu Leu Thr Lys 1430  $$1435\$ 

Glu Met Ala His Leu Glu Gly Leu Met Lys Asp Leu Asn Ala Ile 1445 1450 1455

Thr Thr Ala 1460

<210> 190 <211> 736 <212> PRT

<213> Homo sapiens

<400> 190

Met Val Val Thr Arg Ser Ala Arg Ala Lys Ala Ser Ile Gln Ala Ala 1 5 10 15

Ser Ala Glu Ser Ser Gly Gln Lys Ser Phe Ala Ala Asn Gly Ile Gln 20 25 30

Ala His Pro Glu Ser Ser Thr Gly Ser Asp Ala Arg Thr Thr Asp Glu 35 40 45

Ser Gln Thr Thr Gly Lys Gln Ser Leu Ile Pro Arg Thr Pro Lys Ala Page 303

50 55

Arg Lys Ser Lys Ser Arg Thr Thr Gly Ser Leu Pro Lys Gly Thr Glu 65 70 75 80

Pro Ser Thr Asp Gly Glu Thr Ser Glu Ala Glu Ser Asn Tyr Ser Val $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Ser Glu His His Asp Thr Ile Leu Arg Val Thr Arg Arg Arg Gln Ile  $100 \hspace{1cm} 105 \hspace{1cm} 105$ 

Leu Ile Ala Cys Ser Pro Val Ser Ser Val Arg Lys Lys Pro Lys Val 115 120 125

Thr Pro Thr Lys Glu Ser Tyr Thr Glu Glu Ile Val Ser Glu Ala Glu 130 135 140

Ser His Val Ser Gly Ile Ser Arg Ile Val Leu Pro Thr Glu Lys Thr 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}155\phantom{\bigg|}$ 

Thr Gly Ala Arg Arg Ser Lys Ala Lys Ser Leu Thr Asp Pro Ser Gln 165 170 175

Glu Ser His Thr Glu Ala Ile Ser Asp Ala Glu Thr Ser Ser Ser Asp 180 185 190

Ile Ser Phe Ser Gly Ile Ala Thr Arg Arg Thr Arg Ser Met Gln Arg 195 200 205

Lys Leu Lys Ala Gln Thr Glu Lys Lys Asp Ser Lys Ile Val Pro Gly 210 215 220

Asn Glu Lys Gln Ile Val Gly Thr Pro Val Asn Ser Glu Asp Ser Asp 225 230 235 240

Thr Arg Gln Thr Ser His Leu Gln Ala Arg Ser Leu Ser Glu Ile Asn 245 250 255

Lys Pro Asn Phe Tyr Asn Asn Asp Phe Asp Asp Asp Phe Ser His Arg 260 265 270

Ser Ser Glu Asn Ile Leu Thr Val His Glu Gln Ala Asn Val Glu Ser  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285 \hspace{1.5cm}$ 

Leu Lys Glu Thr Lys Gln Asn Cys Lys Asp Leu Asp Glu Asp Ala Asn 290 295 300

Gly Ile Thr Asp Glu Gly Lys Glu Ile Asn Glu Lys Ser Ser Gln Leu 305 310 315 320

Lys Asn Leu Ser Glu Leu Gln Asp Thr Ser Leu Gln Gln Leu Val Ser 325 330 335

Gln Arg His Ser Thr Pro Gln Asn Lys Asn Ala Val Ser Val His Ser 340 345 350

Asn Leu Asn Ser Glu Ala Val Met Lys Ser Leu Thr Gln Thr Phe Ala 355  $\phantom{\bigg|}360\phantom{\bigg|}365\phantom{\bigg|}$ 

Thr Val Glu Val Gly Arg Trp Asn Asn Asn Lys Lys Ser Pro Ile Lys 370 375 380

Ala Ser Asp Leu Thr Lys Phe Gly Asp Cys Gly Gly Ser Asp Asp Glu 385 390 395 400

Glu Glu Ser Thr Val Ile Ser Val Ser Glu Asp Met Asn Ser Glu Gly 405 410 415

Asn Val Asp Phe Glu Cys Asp Thr Lys Leu Tyr Thr Ser Ala Pro Asn 420 425 430

Thr Ser Gln Gly Lys Asp Asn Ser Val Leu Leu Val Leu Ser Ser Asp 435 440 445

Glu Ser Gln Gln Ser Glu Asn Ser Glu Asn Glu Glu Asp Thr Leu Cys 450 455 460

Phe Val Glu Asn Ser Gly Gln Arg Glu Ser Leu Ser Gly Asp Thr Gly 465 470 475 480

Ser Leu Ser Cys Asp Asn Ala Leu Phe Val Ile Asp Thr Thr Pro Gly 485 490 495

Met Ser Ala Asp Lys Asn Phe Tyr Leu Glu Glu Glu Asp Lys Ala Ser 500 505 510

Glu Val Ala Ile Glu Glu Glu Lys Glu Glu Glu Glu Asp Glu Lys Ser 515 520 525

Glu Glu Asp Ser Ser Asp His Asp Glu Asn Glu Asp Glu Phe Ser Asp 530 535 540

Glu Glu Asp Phe Leu Asn Ser Thr Lys Ala Lys Leu Leu Lys Leu Thr 545 550 560

Ser Ser Ser Ile Asp Pro Gly Leu Ser Ile Lys Gln Leu Gly Gly Leu 565 570 575

Tyr Ile Asn Phe Asn Ala Asp Lys Leu Gln Ser Asn Lys Arg Thr Leu 580 585 590

Thr Gln Ile Lys Glu Lys Lys Lys Asn Glu Leu Leu Gln Lys Ala Val 595 600 605

Ile Thr Pro Asp Phe Glu Lys Asn His Cys Val Pro Pro Tyr Ser Glu 610 615 620

Ser Lys Tyr Gln Leu Gln Lys Lys Arg Arg Lys Glu Arg Gln Lys Thr 625 630 635 640

Ala Gly Asp Gly Trp Phe Gly Met Lys Ala Pro Glu Met Thr Asn Glu 645 650 655

Leu Lys Asn Asp Leu Lys Ala Leu Lys Met Arg Ala Ser Met Asp Pro 660 665 670

Lys Arg Phe Tyr Lys Lys Asn Asp Arg Asp Gly Phe Pro Lys Tyr Phe 675 680 685

Gln Ile Gly Thr Ile Val Asp Asn Pro Ala Asp Phe Tyr His Ser Arg  $690 \hspace{1.5cm} 695 \hspace{1.5cm} 700$ 

Ile Pro Lys Lys Gln Arg Lys Arg Thr Ile Val Glu Asp Cys Trp Leu 705  $\phantom{\bigg|}$  710  $\phantom{\bigg|}$  720

Ile Leu Asn Ser Glu Ile Gln Pro Lys Glu Val Leu Arg Asp His Gly 725 730 735

<210> 191

<211> 465

<212> PRT

<213> Homo sapiens

<400> 191

Met Ala Met Thr Gly Ser Thr Pro Cys Ser Ser Met Ser Asn His Thr 1  $\phantom{\bigg|}10\phantom{\bigg|}$ 

Lys Glu Arg Val Thr Met Thr Lys Val Thr Leu Glu Asn Phe Tyr Ser 20

Asn Leu Ile Ala Gln His Glu Glu Arg Glu Met Arg Gln Lys Lys Leu  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Glu Lys Val Met Glu Glu Glu Glu Lys Asp Glu Glu Lys Arg Leu 50  $\,$  55  $\,$  60  $\,$ 

Arg Arg Ser Ala His Ala Arg Lys Glu Thr Glu Phe Leu Arg Leu Lys 65 70 75 80

Arg Thr Arg Leu Gly Leu Glu Asp Phe Glu Ser Leu Lys Val Ile Gly 85 90 95

Arg Gly Ala Phe Gly Glu Val Arg Leu Val Gln Lys Lys Asp Thr Gly  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

His Val Tyr Ala Met Lys Ile Leu Arg Lys Ala Asp Met Leu Glu Lys 115 120 125

Glu Gln Val Gly His Ile Arg Ala Glu Arg Asp Ile Leu Val Glu Ala 130 135 140

Asp Ser Leu Trp Val Val Lys Met Phe Tyr Ser Phe Gln Asp Lys Leu 145 150 155 160

Asn Leu Tyr Leu Ile Met Glu Phe Leu Pro Gly Gly Asp Met Met Thr 165 170 . 175

Leu Leu Met Lys Lys Asp Thr Leu Thr Glu Glu Glu Thr Gln Phe Tyr 180 185 190

Ile Ala Glu Thr Val Leu Ala Ile Asp Ser Ile His Gln Leu Gly Phe 195  $\phantom{\bigg|}200\phantom{\bigg|}$  205

Ile His Arg Asp Ile Lys Pro Asp Asn Leu Leu Leu Asp Ser Lys Gly 210 215 220

His Val Lys Leu Ser Asp Phe Gly Leu Cys Thr Gly Leu Lys Lys Ala 225 230 235 240

His Arg Thr Glu Phe Tyr Arg Asn Leu Asn His Ser Leu Pro Ser Asp 245 250 255

Phe Thr Phe Gln Asn Met Asn Ser Lys Arg Lys Ala Glu Thr Trp Lys 260 265 270

Arg Asn Arg Arg Gln Leu Ala Phe Ser Thr Val Gly Thr Pro Asp Tyr 275 280 285

Ile Ala Pro Glu Val Phe Met Gln Thr Gly Tyr Asn Lys Leu Cys Asp 290 295 300

Trp Trp Ser Leu Gly Val Ile Met Tyr Glu Met Leu Ile Gly Tyr Pro 305 310 315 320

Pro Phe Cys Ser Glu Thr Pro Gln Glu Thr Tyr Lys Lys Val Met Asn 325 330 335

Trp Lys Glu Thr Leu Thr Phe Pro Pro Glu Val Pro Ile Ser Glu Lys 340 345 350

Ala Lys Asp Leu Ile Leu Arg Phe Cys Cys Glu Trp Glu His Arg Ile 355 360 365

Gly Ala Pro Gly Val Glu Glu Ile Lys Ser Asn Ser Phe Phe Glu Gly 370 375 380

Val Asp Trp Glu His Ile Arg Glu Arg Pro Ala Ala Ile Ser Ile Glu 385 390 395 400

Ile Lys Ser Ile Asp Asp Thr Ser Asn Phe Asp Glu Phe Pro Glu Ser 405 410 415

Asp Ile Leu Lys Pro Thr Val Ala Thr Ser Asn His Pro Glu Thr Asp 420 425 430

Tyr Lys Asn Lys Asp Trp Val Phe Ile Asn Tyr Thr Tyr Lys Arg Phe 435 440 445

Glu Gly Leu Thr Ala Arg Gly Ala Ile Pro Ser Tyr Met Lys Ala Ala 450  $\phantom{\bigg|}455\phantom{\bigg|}$ 

<210> 192

PRT

<213> Homo sapiens

Met Thr Tyr Phe Pro Leu Gly Arg Tyr Pro Val Val Gly Leu Leu Asp 1  $\phantom{\Big|}$  10  $\phantom{\Big|}$  15

Gln Met Val Val Leu Ser Thr Phe Ser Ser Leu Lys Asn Leu His Ile  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Val Phe His Ser Gly Cys Thr Ser Leu His Ser His Gln Leu Cys Lys  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Arg Val Pro Phe Ser Pro His Pro Arg Gln His Leu Leu Phe Phe Asp 50 55 60

Phe Trp Ile Lys Ala Ile Leu Ala Glu 65 70

<210> 193

<211> 410 <212> PRT

<213> Homo sapiens

<400> 193

Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu 1 5 5 10 15

Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Leu Glu Leu Asn 20 25 30

Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met 35 45

Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val 50 60

Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly 65 70 75 80

Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe 85 90 95

Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp 115 120 125

Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg 130 135 140

Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu 145 150 150 160

Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe 165 170 175

Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp 180 185 190

Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro  $195 \ \ \, 200 \ \ \, 205$ 

Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser 210 215 220

Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln 225 230 235 240

Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro 245 250 255

Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu 260 265 270

Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val 275 280 285

Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr 290 295 300

Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr 305 310 315 320

Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr 325 330 335

Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val  $340 \hspace{1.5cm} 345 \hspace{1.5cm} 350 \hspace{1.5cm}$ 

Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Glu Cys 355 360 365

Ser Leu Asp Asp Asp Thr Ile Leu Ile Pro Ile Ile Val Gly Ala Gly 370 375 380

Leu Ser Gly Leu Ile Ile Val Ile Val Ile Ala Tyr Val Ile Gly Arg 385 390 395 400

Arg Lys Ser Tyr Ala Gly Tyr Gln Thr Leu 405 410

194 480

<211> PRT

Homo sapiens

Met Ala Gly Gly Gly Asp Leu Ser Thr Arg Arg Leu Asn Glu Cys 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Ile Ser Pro Val Ala Asn Glu Met Asn His Leu Pro Ala His Ser His 20 25 30

Asp Leu Gln Arg Met Phe Thr Glu Asp Gln Gly Val Asp Asp Arg Leu  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Leu Tyr Asp Ile Val Phe Lys His Phe Lys Arg Asn Lys Val Glu Ile 50  $\phantom{-}$  55  $\phantom{-}$  60

Ser Asn Ala Ile Lys Lys Thr Phe Pro Phe Leu Glu Gly Leu Arg Asp 65 70 75 80

Arg Asp Leu Ile Thr Asn Lys Met Phe Glu Asp Ser Gln Asp Ser Cys 85 90 95

Arg Asn Leu Val Pro Val Gln Arg Val Val Tyr Asn Val Leu Ser Glu 100 105 110

Leu Glu Lys Thr Phe Asn Leu Pro Val Leu Glu Ala Leu Phe Ser Asp 115 120 125

Val Asn Met Gln Glu Tyr Pro Asp Leu Ile His Ile Tyr Lys Gly Phe 130 140

Glu Asn Val Ile His Asp Lys Leu Pro Leu Gln Glu Ser Glu Glu 145 150 150 155 160

Glu Arg Glu Glu Arg Ser Gly Leu Gln Leu Ser Leu Glu Gln Gly Thr \$165\$ \$170\$ 175

Gly Glu Asn Ser Phe Arg Ser Leu Thr Trp Pro Pro Ser Gly Ser Pro 180 185 190

Ser His Ala Gly Thr Thr Pro Pro Glu Asn Gly Leu Ser Glu His Pro 195 200 205

Cys Glu Thr Glu Gln Ile Asn Ala Lys Arg Lys Asp Thr Thr Ser Asp 210 215 220

Lys Asp Asp Ser Leu Gly Ser Gln Gln Thr Asn Glu Gln Cys Ala Gln 225 230 235 240

Lys Ala Glu Pro Thr Glu Ser Cys Glu Gln Ile Ala Val Gln Val Asn  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255 \hspace{1.5cm}$ 

Asn Gly Asp Ala Gly Arg Glu Met Pro Cys Pro Leu Pro Cys Asp Glu 260 265 270

Glu Ser Pro Glu Ala Glu Leu His Asn His Gly Ile Gln Ile Asn Ser  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285 \hspace{1.5cm}$ 

Cys Ser Val Arg Leu Val Asp Ile Lys Lys Glu Lys Pro Phe Ser Asn 290  $\phantom{\bigg|}295\phantom{\bigg|}$  300

Ser Lys Val Glu Cys Gln Ala Gln Ala Arg Thr His His Asn Gln Ala 305 310 310 320

Ser Asp Ile Ile Val Ile Ser Ser Glu Asp Ser Glu Gly Ser Thr Asp 325 330 335

Val Asp Glu Pro Leu Glu Val Phe Ile Ser Ala Pro Arg Ser Glu Pro 340 345 350

Val Ile Asn Asn Asp Asn Pro Leu Glu Ser Asn Asp Glu Lys Glu Gly 355 360 365

Gln Glu Ala Thr Cys Ser Arg Pro Gln Ile Val Pro Glu Pro Met Asp 370 375 380

Phe Arg Lys Leu Ser Thr Phe Arg Glu Ser Phe Lys Lys Arg Val 1le 385 390 395 400

Gly Gln Asp His Asp Phe Ser Glu Ser Ser Glu Glu Glu Ala Pro Ala 415

Glu Ala Ser Ser Gly Ala Leu Arg Ser Lys His Gly Glu Lys Ala Pro  $420 \hspace{1.5cm} 425 \hspace{1.5cm} 430$ 

Met Thr Ser Arg Ser Thr Ser Thr Trp Arg Ile Pro Ser Arg Lys Arg 435 440 445

Arg Phe Ser Ser Ser Asp Phe Ser Asp Leu Ser Asn Gly Glu Glu Leu 450 460

Gln Glu Thr Cys Ser Ser Ser Leu Arg Arg Gly Ser Gly Lys Glu Asp 465 470 475 480

210> 195

<211> 339 <212> PRT

<213> Homo sapiens

<400> 195

Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn 1 5 10 15

Ala Arg Ser Arg Pro Ser Phe His Pro Leu Ser Asp Glu Leu Val Asn 20 25 30

Tyr Val Asn Lys Arg Asn Thr Thr Trp Gln Ala Gly His Asn Phe Tyr  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Asn Val Asp Met Ser Tyr Leu Lys Arg Leu Cys Gly Thr Phe Leu Gly 50 60

Gly Pro Lys Pro Pro Gln Arg Val Met Phe Thr Glu Asp Leu Lys Leu 65 70 70 75 80

Pro Ala Ser Phe Asp Ala Arg Glu Gln Trp Pro Gln Cys Pro Thr Ile  $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Lys Glu Ile Arg Asp Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Gly 100  $\,$  105  $\,$  110  $\,$ 

Ala Val Glu Ala Ile Ser Asp Arg Ile Cys Ile His Thr Asn Ala His 115  $\phantom{\bigg|}$  120  $\phantom{\bigg|}$  125

Val Ser Val Glu Val Ser Ala Glu Asp Leu Leu Thr Cys Cys Gly Ser 130  $$135\$ 

Met Cys Gly Asp Gly Cys Asn Gly Gly Tyr Pro Ala Glu Ala Trp Asn 145 150 150 155 160

Phe Trp Thr Arg Lys Gly Leu Val Ser Gly Gly Leu Tyr Glu Ser His 165 170 175

Val Gly Cys Arg Pro Tyr Ser Ile Pro Pro Cys Glu His His Val Asn 180 185 190

Gly Ser Arg Pro Pro Cys Thr Gly Glu Gly Asp Thr Pro Lys Cys Ser 195 200 205

Tyr Gly Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met 225 230 240

Ala Glu Ile Tyr Lys Asn Gly Pro Val Glu Gly Ala Phe Ser Val Tyr 245 250 255

Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr Gly 260 265 270

Glu Met Met Gly Gly His Ala Ile Arg Ile Leu Gly Trp Gly Val Glu 275 280 285

Asn Gly Thr Pro Tyr Trp Leu Val Ala Asn Ser Trp Asn Thr Asp Trp 290 295 300

Gly Asp Asn Gly Phe Phe Lys Ile Leu Arg Gly Gln Asp His Cys Gly 305 310 315 320

Ile Glu Ser Glu Val Val Ala Gly Ile Pro Arg Thr Asp Gln Tyr Trp 325 330 335

Glu Lys Ile

210> 196

<211> 2328

<212> PRT

<213> Homo sapiens

<400> 196

Lys Ser Lys Arg Gln Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val 1 5 10 15

Ala Val Ser Gln Ser Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr 20 25 30

Gln Ile Asn Gln Gln Trp Glu Arg Thr Tyr Leu Gly Asn Val Leu Val 35 40 45

Cys Thr Cys Tyr Gly Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro 50 60

Glu Ala Glu Glu Thr Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg 65 70 75 80

Val Gly Asp Thr Tyr Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys 85 90 95

Thr Cys Ile Gly Ala Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn  $100 \hspace{1cm} 105 \hspace{1cm} 105$ 

Arg Cys His Glu Gly Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg 115 120 125

Arg Pro His Glu Thr Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly 130 135 140

Asn Gly Lys Gly Glu Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe 145 150 150 160

Asp His Ala Ala Gly Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys 165 170 175

Pro Tyr Gln Gly Trp Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly 180 185 190

Ser Gly Arg Ile Thr Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp 195 200 205 Thr Arg Thr Ser Tyr Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn 210 215 220 Arg Gly Asn Leu Leu Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly 225 230 235 240 Trp Lys Cys Glu Arg His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser 245 250 255 Gly Pro Phe Thr Asp Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$ Pro Gln Pro Pro Pro Tyr Gly His Cys Val Thr Asp Ser Gly Val Val 275 280 285 Tyr Ser Val Gly Met Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met 290 295 300 Leu Cys Thr Cys Leu Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val 305 310 315 320 Thr Gln Thr Tyr Gly Gly Asn Leu Asn Gly Glu Pro Cys Val Leu Pro 325 330 335 Phe Thr Tyr Asn Gly Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg 340 345 350Gln Asp Gly His Leu Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp  $355 \hspace{1cm} 360 \hspace{1cm} 365$ Gln Lys Tyr Ser Phe Cys Thr Asp His Thr Val Leu Val Gln Thr Gln 370 \$375\$Gly Gly Asn Ser Asn Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn 385 390 395 400 Asn His Asn Tyr Thr Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met  $405 \hspace{1.5cm} 410 \hspace{1.5cm} 415$ Lys Trp Cys Gly Thr Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly 420 425 430Phe Cys Pro Met Ala Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly 435 440 445 Val Met Tyr Arg Ile Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly 450 460 His Met Met Arg Cys Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr 465 470 475 480 Cys Ile Ala Tyr Ser Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile 485 490 495 Thr Tyr Asn Val Asn Asp Thr Phe His Lys Arg His Glu Glu Gly His

Page 313

500 505 510

Met Leu Asn Cys Thr Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys 515 520 525

Asp Pro Val Asp Gln Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln 530 535 540

Ile Gly Asp Ser Trp Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys 545 550 555 560

Tyr Cys Tyr Gly Arg Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln 565 570 575

Thr Tyr Pro Ser Ser Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr 580 585 590

Pro Ser Gln Pro Asn Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro 595 600 605

Ser His Ile Ser Lys Tyr Ile Leu Arg Trp Arg Pro Lys Asn Ser Val 610 615 620

Gly Arg Trp Lys Glu Ala Thr Ile Pro Gly His Leu Asn Ser Tyr Thr 625  $\,$  630  $\,$  635  $\,$  640

Ile Lys Gly Leu Lys Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser 645 650 655

Ile Gln Gln Tyr Gly His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670$ 

Thr Ser Thr Ser Thr Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr 675  $\,$  680  $\,$  685

Thr Pro Phe Ser Pro Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile 690 695 700

Thr Ala Ser Ser Phe Val Val Ser Trp Val Ser Ala Ser Asp Thr Val 705 710 715 720

Ser Gly Phe Arg Val Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro  $725 \hspace{1cm} 730 \hspace{1cm} 735$ 

Gln Tyr Leu Asp Leu Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp  $740 \hspace{1.5cm} 745 \hspace{1.5cm} 750$ 

Leu Leu Pro Gly Arg Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu  $755 \hspace{1.5cm} 760 \hspace{1.5cm} 765$ 

Asp Gly Glu Gln Ser Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro 770 780

Asp Ala Pro Pro Asp Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile 785 790 795 800

Val Val Arg Trp Ser Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile 805 810 815

Val Tyr Ser Pro Ser Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro 820 825 830

Glu Thr Ala Asn Ser Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln 835 840 845

Tyr Asn Ile Thr Ile Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro 850 860

Val Val Ile Gln Gln Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val 865 870 875 880

Pro Ser Pro Arg Asp Leu Gln Phe Val Glu Val Thr Asp Val Lys Val 885 890 895

Thr Ile Met Trp Thr Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val 900 905 910

Asp Val Ile Pro Val Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro 915 920 925

Ile Ser Arg Asn Thr Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val 930 935 940

Thr Tyr Tyr Phe Lys Val Phe Ala Val Ser His Gly Arg Glu Ser Lys 945 950 955 960

Pro Leu Thr Ala Gln Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu 965 970 975

Gln Phe Val Asn Glu Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro 980 985 990

Pro Arg Ala Gln Ile Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg 995 1000 1005

Arg Gly Gln Pro Arg Gln Tyr Asn Val Gly Pro Ser Val Ser Lys 1010 1015 1020

Tyr Pro Leu Arg Asn Leu Gln Pro Ala Ser Glu Tyr Thr Val Ser 1025 1030 1035

Leu Val Ala Ile Lys Gly Asn Gln Glu Ser Pro Lys Ala Thr Gly 1040 1045

Val Phe Thr Thr Leu Gln Pro Gly Ser Ser Ile Pro Pro Tyr Asn 1055 1060 1065

Pro Arg Ile Gly Phe Lys Leu Gly Val Arg Pro Ser Gln Gly Gly 1085 1090 1095

Glu Ala Pro Arg Glu Val Thr Ser Asp Ser Gly Ser Ile Val Val 1100  $$1105\$ 

Ser Gly Leu Thr Pro Gly Val Glu Tyr Val Tyr Thr Ile Gln Val 1115 1120 1125

Leu Arg Asp Gly Gln Glu Arg Asp Ala Pro Ile Val Asn Lys Val 1130 1140

Val Thr Pro Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala Asn 1145 1150 1155

Pro Asp Thr Gly Val Leu Thr Val Ser Trp Glu Arg Ser Thr Thr 1160  $\,$  1170

Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly 1175 1180 1185

Gln Gln Gly Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser 1190 . 1195 1200

Ser Cys Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val 1205 1210 1215

Ser Val Tyr Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser 1220 1225

Asp Thr Ile Ile Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe 1235 1240 1245

Thr Asn Ile Gly Pro Asp Thr Met Arg Val Thr Trp Ala Pro Pro 1250 1260

Pro Ser Ile Asp Leu Thr Asn Phe Leu Val Arg Tyr Ser Pro Val 1265 1270 1275

Lys Asn Glu Glu Asp Val Ala Glu Leu Ser Ile Ser Pro Ser Asp 1280 1285 1290

Asn Ala Val Val Leu Thr Asn Leu Leu Pro Gly Thr Glu Tyr Val 1295 1300 1305

Val Ser Val Ser Ser Val Tyr Glu Gln His Glu Ser Thr Pro Leu 1310 1315 1320

Arg Gly Arg Gln Lys Thr Gly Leu Asp Ser Pro Thr Gly Ile Asp 1325 1330 1335

Phe Ser Asp Ile Thr Ala Asn Ser Phe Thr Val His Trp Ile Ala 1340 1345 1350

Pro Arg Ala Thr Ile Thr Gly Tyr Arg Ile Arg His His Pro Glu 1355 1360 1365

His Phe Ser Gly Arg Pro Arg Glu Asp Arg Val Pro His Ser Arg 1370 1375 1380

Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro Gly Thr Glu Tyr Val 1385 1390 1395

Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu Ser Pro Leu Leu 1400 1405 1410

Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg Asp Leu Glu 1415 1420 1425

Val Val 7	Ala Al	a Thr	Pro	Thr 1435	Ser	Leu	Leu	Ile	Ser 1440	Trp	Asp	Ala
Pro Ala 1445	Val Th	r Val		Tyr 1450		Arg	Ile	Thr	Tyr 1455	Gly	Glu	Thr
Gly Gly 1	Asn Se	r Pro		Gln 1465		Phe	Thr		Pro 1470	Gly	Ser	Lys
Ser Thr 1 1475	Ala Th	r Ile	Ser	Gly 1480	Leu	Lys	Pro	Gly	Val 1485	Asp	Туr	Thr
Ile Thr 1	Val Ty	r Ala		Thr 1495		Arg	Gly		Ser 1500	Pro	Ala	Ser
Ser Lys 1505	Pro Il	e Ser	Ile	Asn 1510		Arg	Thr	Glu	Ile 1515	Asp	Lys	Pro
Ser Gln I 1520	Met Gl	n Val		Asp 1525		Gln	Asp		Ser 1530	Ile	Ser	Val
Lys Trp 1	Leu Pr	o Ser	Ser	Ser 1540	Pro	Val	Thr	Gly	Туг 1545	Arg	Val	Thr
Thr Thr 1550	Pro Ly	s Asn	Gly	Pro 1555		Pro	Thr	Lys	Thr 1560		Thr	Ala
Gly Pro 1565	Asp Gl	n Thr		Met 1570	Thr	Ile	Glu	Gly	Leu 1575	Gln	Pro	Thr
Val Glu 1 1580	Tyr Va	l Val	Ser	Val 1585		Ala	Gln	Asn	Pro 1590	Ser	Gly	Glu
Ser Gln 1595	Pro Le	u Val	Gln	Thr 1600		Val	Thr	Asn	Ile 1605	Asp	Arg	Pro
Lys Gly 1	Leu Al	a Phe	Thr	Asp 1615	Val	Asp	Val		Ser 1620		Lys	Ile
Ala Trp 1625	Glu Se	r Pro	Gln	Gly 1630		Val	Ser	Arg	Tyr 1635	Arg	Val	Thr
Tyr Ser 1640	Ser Pr	o Glu	Asp	Gly 1645	Ile	His	Glu	Leu	Phe 1650		Ala	Pro
Asp Gly (	Glu Gl	u Asp	Thr	Ala 1660	Glu	Leu	Gln	Gly	Leu 1665	Arg	Pro	Gly
Ser Glu ' 1670	Tyr Th	r Val	Ser	Val 1675		Ala	Leu	His	Asp 1680	Asp	Met	Glu
Ser Gln 1 1685	Pro Le	u Ile	Gly	Thr 1690	Gln	Ser	Thr	Ala	Ile 1695	Pro	Ala	Pro
Thr Asp 1 1700	Leu Ly	s Phe	Thr	Gln 1705		Thr	Pro	Thr	Ser 1710	Leu	Ser	Ala
Gln Trp	Thr Pr	o Pro	Asn	Val	Gln	Leu	Thr	-	Tyr ge 31	-	Val	Arg

1715 1720 1725

Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu 1730 1740

Ala Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala 1745 1750 1755

Thr Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr 1760 1765

Ser Arg Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser 1775 1780 1785

Pro Pro Arg Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile 1790 1795 1800

Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln 1805 1810 1815

Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr 1820 1830

Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro 1835  $\phantom{0}$  1840 .

Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala 1850 1860

Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala 1865 1870 1875

Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu 1880 1885

Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile 1895 1900 1905

Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg 1910 1915 1920

Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro 1925 1930 1935

Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln 1940 1950

Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro 1955 1960 1965

Gln Leu Val Thr Leu Pro His Pro Asn Leu His Gly Pro Glu Ile 1970 1975 1980

Leu Asp Val Pro Ser Thr Val Gln Lys Thr Pro Phe Val Thr His 1985 1995

Pro Gly Tyr Asp Thr Gly Asn Gly Ile Gln Leu Pro Gly Thr Ser 2000 2005 2010

Gly	Gln 2015	Gln	Pro	Ser	Val	Gly 2020	Gln	Gln	Met		rne 2025	GIU	GIU	Hls
Gly	Phe 2030	Arg	Arg	Thr	Thr	Pro 2035	Pro	Thr	Thr	Ala	Thr 2040	Pro	Ile	Arg
His	Arg 2045	Pro	Arg	Pro	Tyr	Pro 2050	Pro	Asn	Val		Gln 2055	Glu	Ala	Leu
Ser	Gln 2060	Thr	Thr	Ile	Ser	Trp 2065	Ala	Pro	Phe		Asp 2070	Thr	Ser	Glu
Tyr	Ile 2075	Ile	Ser	Cys	His	Pro 2080	Val	Gly	Thr		Glu 2085	Glu	Pro	Leu
Gln	Phe 2090	Arg	Val	Pro	Gly	Thr 2095	Ser	Thr	Ser		Thr 2100	Leu	Thr	Gly
Leu	Thr 2105	Arg	Gly	Ala	Thr	туг 2110	Asn	Ile	Ile	Val	Glu 2115	Ala	Leu	Lys
Asp	Gln 2120	Gln	Arg	His	Lys	Val 2125	Arg	Glu	Glu		Val 2130	Thr	Val	Gly
Asn	Ser 2135	Val	Asn	Glu	Gly	Leu 2140	Asn	Gln	Pro	Thr	Asp 2145	Asp	Ser	Cys
Phe	Asp 2150		Tyr	Thr	Val	Ser 2155	His	туг	Ala	Val	Gly 2160	Asp	Glu	Trp
Glu	Arg 2165		Ser	Glu	Ser	Gly 2170		Lys	Leu		Cys 2175	Gln	Cys	Leu
Gly	Phe 2180	Gly	Ser	Gly	His	Phe 2185	Arg	Cys	Asp	Ser	Ser 2190	Arg	Trp	Cys
His	Asp 2195		Gly	Val	Asn	Tyr 2200		Ile	Gly	Glu	Lys 2205	Trp	Asp	Arg
Gln	Gly 2210	Glu	Asn	Gly	Gln	Met 2215	Met	Ser	Cys	Thr	Cys 2220	Leu	Gly	Asn
Gly	Lys 2225	Gly	Glu	Phe	Lys	Cys 2230	Asp	Pro	His	Glu	Ala 2235	Thr	Cys	Tyr
Asp	Asp 2240	Gly	Lys	Thr	Tyr	His 2245	Val	Gly	Glu	Gln	Trp 2250	Gln	Lys	Glu
Tyr	Leu 2255	Gly	Ala	Ile	Cys	Ser 2260		Thr	Суз	Phe	Gly 2265	Gly	Gln	Arg
Gly	Trp 2270	Arg	Cys	Asp	Asn	Cys 2275	Arg	Arg	Pro	Gly	Gly 2280	Glu	Pro	Ser
Pro	Glu 2285	Gly	Thr	Thr	Gly	Gln 2290		Tyr	Asn	Gln	Tyr 2295	Ser	Gln	Arg
Tyr	His 2300	Gln	Arg	Thr	Asn	Thr 2305	Asn	Val	Asn	Cys	Pro 2310	Ile	Glu	Cys

Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp Ser Arg Glu 2315 2320 2325

<210> 197

<211> 165 <212> PRT

<213> Homo sapiens

<400> 197

Met Leu Met Pro Lys Lys Asn Arg Ile Ala Ile Tyr Glu Leu Leu Phe 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Lys Glu Gly Val Met Val Ala Lys Lys Asp Val His Met Pro Lys His 20 25 30

Pro Glu Leu Ala Asp Lys Asn Val Pro Asn Leu His Val Met Lys Ala 35 40 45

Met Gln Ser Leu Lys Ser Arg Gly Tyr Val Lys Glu Gln Phe Ala Trp 50 55 60

Arg His Phe Tyr Trp Tyr Leu Thr Asn Glu Gly Ile Gln Tyr Leu Arg 65 70 75 80

Asp Tyr Leu His Leu Pro Pro Glu Ile Val Pro Ala Thr Leu Arg Arg 85 90 95

Ser Arg Pro Glu Thr Gly Arg Pro Arg Pro Lys Gly Leu Glu Glu Glu 100 \$105\$

Arg Pro Ala Arg Leu Thr Arg Gly Glu Ala Asp Arg Asp Thr Tyr Arg 115 120 125

Arg Ser Ala Val Pro Pro Gly Ala Asp Lys Lys Ala Glu Ala Gly Ala 130 135 140

Gly Ser Ala Thr Glu Phe Gln Phe Arg Gly Gly Phe Gly Arg Gly Arg 145 150 155 160

Gly Gln Pro Pro Gln 165

<210> 198

<211> 154 <212> PRT

<213> Homo sapiens

<400> 198

Met Ala Thr Lys Ala Val Cys Val Leu Lys Gly Asp Gly Pro Val Gln 1  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Gly Ile Ile Asn Phe Glu Gln Lys Glu Ser Asn Gly Pro Val Lys Val  $20 \hspace{1cm} 25 \hspace{1cm} 30 \hspace{1cm}$ 

Trp Gly Ser Ile Lys Gly Leu Thr Glu Gly Leu His Gly Phe His Val  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

His Glu Phe Gly Asp Asn Thr Ala Gly Cys Thr Ser Ala Gly Pro His 50 60

Phe Asn Pro Leu Ser Arg Lys His Gly Gry Pro Lys Asp Gru Gru Arg 65 70 75 80

His Val Gly Asp Leu Gly Asn Val Thr Ala Asp Lys Asp Gly Val Ala 85 90 95

Asp Val Ser Ile Glu Asp Ser Val Ile Ser Leu Ser Gly Asp His Cys 100 ' 105 110

Ile Ile Gly Arg Thr Leu Val Val His Glu Lys Ala Asp Asp Leu Gly 115 120 125

Lys Gly Gly Asn Glu Glu Ser Thr Lys Thr Gly Asn Ala Gly Ser Arg 130 135 140

Leu Ala Cys Gly Val Ile Gly Ile Ala Gln 145

<210> 199

<211> 3256

<212> PRT

<213> Homo sapiens

<400> 199

Met Trp Pro Thr Arg Arg Leu Val Thr Ile Lys Arg Ser Gly Val Asp 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Gly Pro His Phe Pro Leu Ser Leu Ser Thr Cys Leu Phe Gly Arg Gly 20 25 30

Ile Glu Cys Asp Ile Arg Ile Gln Leu Pro Val Val Ser Lys Gln His  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Ser Thr Asn Pro Thr Gln Val Asn Gly Ser Val Ile Asp Glu Pro Val 65  $\phantom{000}70\phantom{000}$  75  $\phantom{0000}80\phantom{000}$ 

Arg Leu Lys His Gly Asp Val Ile Thr Ile Ile Asp Arg Ser Phe Arg 85 90 95

Tyr Glu Asn Glu Ser Leu Gln Asn Gly Arg Lys Ser Thr Glu Phe Pro  $100\,$ 

Arg Lys Ile Arg Glu Gln Glu Pro Ala Arg Arg Val Ser Arg Ser Ser 115 120 125

Phe Ser Ser Asp Pro Asp Glu Lys Ala Gln Asp Ser Lys Ala Tyr Ser 130 135 140

Lys Ile Thr Glu Gly Lys Val Ser Gly Asn Pro Gln Val His Ile Lys 145 150 150 160

Asn Val Lys Glu Asp Ser Thr Ala Asp Asp Ser Lys Asp Ser Val Ala 165 170 175

Gln Gly Thr Thr Asn Val His Ser Ser Glu His Ala Gly Arg Asn Gly 180 185 190

Arg Asn Ala Ala Asp Pro Ile Ser Gly Asp rne Lys Giu ile ser ser 195 200 205

Val Lys Leu Val Ser Arg Tyr Gly Glu Leu Lys Ser Val Pro Thr Thr 210 215 220

Gln Cys Leu Asp Asn Ser Lys Lys Asn Glu Ser Pro Phe Trp Lys Leu 225 230 235 240

Tyr Glu Ser Val Lys Lys Glu Leu Asp Val Lys Ser Gln Lys Glu Asn 245 250 255

Val Leu Gln Tyr Cys Arg Lys Ser Gly Leu Gln Thr Asp Tyr Ala Thr 260 265 270

Glu Lys Glu Ser Ala Asp Gly Leu Gln Gly Glu Thr Gln Leu Leu Val  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285$ 

Ser Arg Lys Ser Arg Pro Lys Ser Gly Gly Ser Gly His Ala Val Ala 290 295 300

Glu Pro Ala Ser Pro Glu Glu Glu Leu Asp Gln Asn Lys Gly Lys Gly 305 310 315 320

Arg Asp Val Glu Ser Val Gln Thr Pro Ser Lys Ala Val Gly Ala Ser 325  $\phantom{\bigg|}330\phantom{\bigg|}$ 

Phe Pro Leu Tyr Glu Pro Ala Lys Met Lys Thr Pro Val Gln Tyr Ser  $340 \hspace{1.5cm} 345 \hspace{1.5cm} 350 \hspace{1.5cm}$ 

Gln Gln Gln Asn Ser Pro Gln Lys His Lys Asn Lys Asp Leu Tyr Thr  $355 \ \ 360 \ \ \ 365$ 

Thr Gly Arg Arg Glu Ser Val Asn Leu Gly Lys Ser Glu Gly Phe Lys 370 380

Ala Gly Asp Lys Thr Leu Thr Pro Arg Lys Leu Ser Thr Arg Asn Arg 385 390 395 400

Thr Pro Ala Lys Val Glu Asp Ala Ala Asp Ser Ala Thr Lys Pro Glu  $405 \hspace{0.25cm} 410 \hspace{0.25cm} 410 \hspace{0.25cm} 415 \hspace{0.25cm}$ 

Asn Leu Ser Ser Lys Thr Arg Gly Ser Ile Pro Thr Asp Val Glu Val 420 425 430

Leu Pro Thr Glu Thr Glu Ile His Asn Glu Pro Phe Leu Thr Leu Trp 435  $\phantom{\bigg|}440\phantom{\bigg|}$ 

Leu Thr Gln Val Glu Arg Lys Ile Gln Lys Asp Ser Leu Ser Lys Pro 450 455 460

Glu Lys Leu Gly Thr Thr Ala Gly Gln Met Cys Ser Gly Leu Pro Gly 465 470 475 480

Leu Ser Ser Val Asp Ile Asn Asn Phe Gly Asp Ser Ile Asn Glu Ser 485 490 495

Glu Gly Ile Pro Leu Lys Arg Arg Arg Val Ser Phe Gly Gly His Leu 500 505 510

Arg Pro Glu Leu Phe Asp Glu Asn Leu Pro Pro Asn Thr Pro Leu Lys 515 525

Arg Gly Glu Ala Pro Thr Lys Arg Lys Ser Leu Val Met His Thr Pro 530 540

Pro Val Leu Lys Lys Ile Ile Lys Glu Gln Pro Gln Pro Ser Gly Lys 545 550 550 560

Gln Glu Ser Gly Ser Glu Ile His Val Glu Val Lys Ala Gln Ser Leu 565 570 575

Asp Gln Arg Arg Ser Ser Cys Lys Thr Ala Pro Ala Ser Ser Ser Lys 595 600 605

Ser Gln Thr Glu Val Pro Lys Arg Gly Glu Glu Arg Val Ala Thr Cys 610 620

Leu Gln Lys Arg Val Ser Ile Ser Arg Ser Gln His Asp Ile Leu Gln 625 630 635 640

Met Ile Cys Ser Lys Arg Arg Ser Gly Ala Ser Glu Ala Asn Leu Ile 645 650 655

Val Ala Lys Ser Trp Ala Asp Val Val Lys Leu Gly Ala Lys Gln Thr  $660 \hspace{1.5cm} 665 \hspace{1.5cm} 670$ 

Gln Thr Lys Val Ile Lys His Gly Pro Gln Arg Ser Met Asn Lys Arg 675 680 685

Gln Arg Arg Pro Ala Thr Pro Lys Lys Pro Val Gly Glu Val His Ser 690 695 700

Gln Phe Ser Thr Gly His Ala Asn Ser Pro Cys Thr Ile Ile Ile Gly 705 710 715 720

Lys Ala His Thr Glu Lys Val His Val Pro Ala Arg Pro Tyr Arg Val 725 730 735

Leu Asn Asn Phe Ile Ser Asn Gln Lys Met Asp Phe Lys Glu Asp Leu 740 745 750

Ser Gly Ile Ala Glu Met Phe Lys Thr Pro Val Lys Glu Gln Pro Gln 755  $\phantom{-}760\phantom{0}$  765

Leu Thr Ser Thr Cys His Ile Ala Ile Ser Asn Ser Glu Asn Leu Leu 770 780

Gly Lys Gln Phe Gln Gly Thr Asp Ser Gly Glu Glu Pro Leu Leu Pro 785 790 795 800

Thr Ser Glu Ser Phe Gly Gly Asn Val Phe Phe Ser Ala Gln Asn Ala  $805 \circ$  810 815

Ala Lys Gln Pro Ser Asp Lys Cys Ser Ala Ser Pro Pro Leu Arg Arg 820 825 830

Gln Cys Ile Arg Glu Asn Gly Asn Val Ala Lys Thr Pro Arg Asn Thr 835 840 845

Tyr Lys Met Thr Ser Leu Glu Thr Lys Thr Ser Asp Thr Glu Thr Glu 850 860

Pro Ser Lys Thr Val Ser Thr Val Asn Arg Ser Gly Arg Ser Thr Glu 865 870 880

Phe Arg Asn Ile Gln Lys Leu Pro Val Glu Ser Lys Ser Glu Glu Thr 885 890 895

As nThr Glu Ile Val Glu Cys Ile Leu Lys Arg Gly Gln Lys Ala Thr 900 905 910

Leu Leu Gln Gln Arg Arg Glu Gly Glu Met Lys Glu Ile Glu Arg Pro $915 \hspace{1.5cm} 920 \hspace{1.5cm} 925$ 

Phe Glu Thr Tyr Lys Glu Asn Ile Glu Leu Lys Glu Asn Asp Glu Lys 930 935 940

Met Lys Ala Met Lys Arg Ser Arg Thr Trp Gly Gln Lys Cys Ala Pro 945 950 955 960

Met Ser Asp Leu Thr Asp Leu Lys Ser Leu Pro Asp Thr Glu Leu Met 965 970 975

Lys Asp Thr Ala Arg Gly Gln Asn Leu Leu Gln Thr Gln Asp His Ala  $980 \hspace{1.5cm} 990 \hspace{1.5cm} 995$ 

Lys Ala Pro Lys Ser Glu Lys Gly Lys Ile Thr Lys Met Pro Cys Gln 995 1000 1005

Ser Leu Gln Pro Glu Pro Ile Asn Thr Pro Thr His Thr Lys Gln 1010 1015 1020

Gln Leu Lys Ala Ser Leu Gly Lys Val Gly Val Lys Glu Glu Leu 1025 1030 1035

Leu Ala Val Gly Lys Phe Thr Arg Thr Ser Gly Glu Thr Thr His 1040 1045 1050

Thr His Arg Glu Pro Ala Gly Asp Gly Lys Ser Ile Arg Thr Phe  $1055 \hspace{1.5cm} 1060 \hspace{1.5cm} 1065$ 

Lys Glu Ser Pro Lys Gln Ile Leu Asp Pro Ala Ala Arg Val Thr 1070 1075 1080

Gly Met Lys Lys Trp Pro Arg Thr Pro Lys Glu Glu Ala Gln Ser 1085 1090 1095

Leu Glu Asp Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr Pro Gly 1100 \$1100\$

Pro Ser Glu Glu Ser Met Thr Asp Glu Lys Thr Thr Lys Ile Ala 1115 1120 1125

Cys Lys Ser Pro Pro Pro Glu Ser Val Asp Thr Pro Thr Ser Thr

1130 1135 1140

Lys Gln Trp Pro Lys Arg Ser Leu Arg Lys Ala Asp Val Glu Glu 1145 1150 1155

Glu Phe Leu Ala Leu Arg Lys Leu Thr Pro Ser Ala Gly Lys Ala 1160 1165 1170

Met Leu Thr Pro Lys Pro Ala Gly Gly Asp Glu Lys Asp Ile Lys 1175 1180 1185

Ala Phe Met Gly Thr Pro Val Gln Lys Leu Asp Leu Ala Gly Thr 1190 1195 1200

Leu Pro Gly Ser Lys Arg Gln Leu Gln Thr Pro Lys Glu Lys Ala 1205 1210 1215

Gln Ala Leu Glu Asp Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr 1220 1225 1230

Pro Gly His Thr Glu Glu Leu Val Ala Ala Gly Lys Thr Thr Lys 1235 1240 1245

Ile Pro Cys Asp Ser Pro Gln Ser Asp Pro Val Asp Thr Pro Thr 1250 1260

Ser Thr Lys Gln Arg Pro Lys Arg Ser Ile Arg Lys Ala Asp Val 1265 1270 1275

Glu Gly Glu Leu Leu Ala Cys Arg Asn Leu Met Pro Ser Ala Gly 1280 1285 1290

Ile Ile Ile Phe Val Gly Thr Pro Val Gln Lys Leu Asp Leu Thr 1310 \$1315\$

Glu Asn Leu Thr Gly Ser Lys Arg Arg Pro Gln Thr Pro Lys Glu 1325 1330 1335

Glu Ala Gln Ala Leu Glu Asp Leu Thr Gly Phe Lys Glu Leu Phe 1340 1350

Gln Thr Pro Gly His Thr Glu Glu Ala Val Ala Ala Gly Lys Thr 1355 1360 1365

Thr Lys Met Pro Cys Glu Ser Ser Pro Pro Glu Ser Ala Asp Thr 1370 1375 1380

Pro Thr Ser Thr Arg Arg Gln Pro Lys Thr Pro Leu Glu Lys Arg 1385 1390 1395

Asp Val Gln Lys Glu Leu Ser Ala Leu Lys Lys Leu Thr Gln Thr 1400 1405 1410

Ser Gly Glu Thr Thr His Thr Asp Lys Val Pro Gly Gly Glu Asp 1415 1420 1425

Lys	Ser 1430		Asn	Ala	Phe	Arg 1435		Thr	Ala	гуз	G1N 1440	гуя	ьeu	Asp
Pro	Ala 1445	Ala	Ser	Val	Thr	Gly 1450		Lys	Arg	His	Pro 1455		Thr	Lys
Glu	Lys 1460	Ala	Gln	Pro	Leu	Glu 1465	Asp	Leu	Ala	Gly	Trp 1470	Lys	Glu	Leu
Phe	Gln 1475	Thr	Pro	Val	Cys	Thr 1480		Lys	Pro	Thr	Thr 1485	His	Glu	Lys
Thr	Thr 1490	Lys	Ile	Ala	Cys	Arg 1495	Ser	Gln	Pro	Asp	Pro 1500	Val	Asp	Thr
Pro	Thr 1505	Ser	Ser	Lys	Pro	Gln 1510		Lys	Arg		Leu 1515	Arg	Lys	Val
Asp	Val 1520	Glu	Glu	Glu	Phe	Phe 1525	Ala	Leu	Arg		Arg 1530		Pro	Ser
Ala	Gly 1535		Ala	Met	His	Thr 1540		Lys	Pro		Val 1545		Gly	Glu
Lys	Asn 1550	Ile	Tyr	Ala	Phe	Met 1555		Thr	Pro	Val	Gln 1560	Lys	Leu	Asp
Leu	Thr 1565	Glu	Asn	Leu	Thr	Gly 1570		Lys	Arg	Arg	Leu 1575	Gln	Thr	Pro
Lys	Glu 1580		Ala	Gln		Leu 1585		Asp	Leu	Ala	Gly 1590		Lys	Glu
Leu	Phe 1595	Gln	Thr	Arg	Gly	Ніs 1600		Glu	Glu	Ser	Met 1605	Thr	Asn	Asp
Lys	Thr 1610	Ala	Lys	Val		Cys 1615		Ser	Ser	Gln	Pro 1620	Asp	Leu	Asp
Lys	Asn 1625	Pro	Ala	Ser	Ser	Lys 1630	Arg	Arg	Leu	Lys	Thr 1635	Ser	Leu	Gly
Lys	Val 1640	Gly	Val	Lys	Glu	Glu 1645	Leu	Leu	Ala	Val	Gly 1650	Lys	Leu	Thr
Gln	Thr 1655	Ser	Gly	Glu	Thr	Thr 1660	His	Thr	His	Thr	Glu 1665	Pro	Thr	Gly
Asp	Gly 1670	Lys	Ser	Met	Lys	Ala 1675	Phe	Met	Glu	Ser	Pro 1680	Lys	Gln	Ile
Leu	Asp 1685	Ser	Ala	Ala	Ser	<b>Leu</b> 1690	Thr	Gly	Ser	Lys	Arg 1695	Gln	Leu	Arg
Thr	Pro 1700	Lys	Gly	Lys	Ser	Glu 1705	Val	Pro	Glu	Asp	Leu 1710	Ala	Gly	Phe
Ile	Glu 1715	Leu	Phe	Gln	Thr	Pro 1720	Ser	His	Thr	Lys	Glu 1725	Ser	Met	Thr

Asn Glu Lys Thr Thr Lys Val Ser Tyr Arg Ala Ser Gln Pro Asp 1730 1735 1740

Leu Val Asp Thr Pro Thr Ser Ser Lys Pro Gln Pro Lys Arg Ser 1745 1750 1755

Leu Arg Lys Ala Asp Thr Glu Glu Glu Phe Leu Ala Phe Arg Lys 1760 1765 1770

Gln Thr Pro Ser Ala Gly Lys Ala Met His Thr Pro Lys Pro Ala 1775 1780 1785

Val Gly Glu Glu Lys Asp Ile Asn Thr Phe Leu Gly Thr Pro Val 1790 1800

Gln Lys Leu Asp Gln Pro Gly Asn Leu Pro Gly Ser Asn Arg Arg 1805 1810 1815

Leu Gln Thr Arg Lys Glu Lys Ala Gln Ala Leu Glu Glu Leu Thr 1820 1830

Ala Asp Glu Lys Thr Thr Lys Lys Ile Leu Cys Lys Ser Pro Gln 1850 1860

Arg Ser Leu Lys Lys Ala Asp Val Glu Glu Glu Phe Leu Ala Phe 1880 1885

Arg Lys Leu Thr Pro Ser Ala Gly Lys Ala Met His Thr Pro Lys  $1895 \ \ \, 1900 \ \ \, 1905$ 

Ala Ala Val Gly Glu Glu Lys Asp Ile Asn Thr Phe Val Gly Thr 1910 1915 1920

Pro Val Glu Lys Leu Asp Leu Leu Gly Asn Leu Pro Gly Ser Lys 1925 1930 1935

Arg Arg Pro Gln Thr Pro Lys Glu Lys Ala Lys Ala Leu Glu Asp 1940 1945 1950

Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr Pro Gly His Thr Glu 1955 1965

Glu Ser Met Thr Asp Asp Lys Ile Thr Glu Val Ser Cys Lys Ser 1970 1975 1980

Pro Gln Pro Asp Pro Val Lys Thr Pro Thr Ser Ser Lys Gln Arg 1985 1990 1995

Leu Lys Ile Ser Leu Gly Lys Val Gly Val Lys Glu Glu Val Leu 2000 2005

Pro Val Gly Lys Leu Thr Gln Thr Ser Gly Lys Thr Thr Gln Thr 2015 2025

His	Arg 2030		Thr	Ala	Gly	Asp 2035		Lys	Ser	Ile	Lys 2040	Ala	Phe	Lys
Glu	Ser 2045	Ala	Lys	Gln		Leu 2050		Pro	Ala	Asn	Tyr 2055		Thr	Gly
Met	Glu 2060	Arg	Trp	Pro	Arg	Thr 2065		Lys	Glu	Glu	Ala 2070	Gln	Ser	Leu
Glu	Asp 2075		Ala	Gly		Lys 2080		Leu	Phe	Gln	Thr 2085	Pro	Asp	His
Thr	Glu 2090	Glu	Ser	Thr	Thr	Asp 2095		Lys	Thr	Thr	Lys 2100	Ile	Ala	Cys
Lys	Ser 2105	Pro	Pro	Pro	Glu	Ser 2110	Met	Asp	Thr	Pro	Thr 2115	Ser	Thr	Arg
Arg	Arg 2120		Lys	Thr		Leu 2125		Lys	Arg	Asp	Ile 2130		Glu	Glu
Leu	Ser 2135	Ala	Leu	Lys	Gln	Leu 2140		Gln	Thr	Thr	His 2145	Thr	Asp	Lys
Val	Pro 2150		Asp	Glu		Lys 2155		Ile	Asn	Val	Phe 2160		Glu	Thr
Ala	Lys 2165	Gln	Lys	Leu	Asp	Pro 2170	Ala	Ala	Ser	Val	Thr 2175	Gly	Ser	Lys
Arg	Gln 2180	Pro	Arg	Thr	Pro	Lys 2185	Gly	Lys	Ala	Gln	Pro 2190	Leu	Glu	Asp
	Ala 2195		Leu	Lys		Leu 2200		Gln	Thr	Pro	Val 2205		Thr	Asp
Lys	Pro 2210		Thr	His	Glu	Lys 2215	Thr	Thr	Lys	Ile	Ala 2220		Arg	Ser
Pro	Gln 2225		Asp	Pro		Gly 2230		Pro	Thr	Ile	Phe 2235		Pro	Gln
Ser	Lys 2240	Arg	Ser	Leu	Arg	Lys 2245	Ala	Asp	Val	Glu	Glu 2250	Glu	Ser	Leu
Ala	Leu 2255	Arg	Lys	Arg	Thr	Pro 2260		Val	Gly	Lys	Ala 2265	Met	Asp	Thr
Pro	Lys 2270	Pro	Ala	Gly	Gly	Asp 2275	Glu	Lys	Asp	Met	Lys 2280	Ala	Phe	Met
Gly	Thr 2285	Pro	Val	Gln	Lys	Leu 2290		Leu	Pro	Gly	Asn 2295	Leu	Pro	Gly
Ser	Lys 2300	Arg	Trp	Pro	Gln	Thr 2305	Pro	Lys	Glu	Lys	Ala 2310	Gln	Ala	Leu
Glu	Asp	Leu	Ala	Gly	Phe	Lys	Glu	Leu	Phe		Thr ge 32		Gly	Thr

	2315					2320					دعدي			
Asp	Lys 2330	Pro	Thr	Thr	Asp	Glu 2335	Lys	Thr	Thr	Lys	11e 2340	Ala	Cys	Lys
Ser	Pro 2345	Gln	Pro	Asp	Pro	Val 2350	Asp	Thr	Pro	Ala	Ser 2355	Thr	Lys	Gln
Arg	Pro 2360	Lys	Arg	Asn	Leu	Arg 2365	Lys	Ala	Asp	Val	Glu 2370	Glu	Glu	Phe
Leu	Ala 2375	Leu	Arg	Lys	Arg	Thr 2380	Pro	Ser	Ala	Gly	Lys 2385	Ala	Met	Asp
Thr	Pro 2390		Pro	Ala		Ser 2395		Glu	Lys	Asn	Ile 2400	Asn	Thr	Phe
Val	Glu 2405	Thr	Pro	Val	Gln	Lys 2410	Leu	Asp	Leu	Leu	Gly 2415	Asn	Leu	Pro
Gly	Ser 2420		Arg	Gln		Gln 2425		Pro	Lys	Glu	Lys 2430	Ala	Glu	Ala
Leu	Glu 2435		Leu	Val	Gly	Phe 2440		Glu	Leu	Phe	Gln 2445	Thr	Pro	Gly
His	Thr 2450		Glu	Ser	Met	Thr 2455	Asp	Asp	Lys	Ile	Thr 2460	Glu	Val	Ser
Cys	Lys 2465		Pro	Gln	Pro	Glu 2470		Phe	Lys	Thr	Ser 2475	Arg	Ser	Ser
Lys	Gln 2480		Leu	Lys	Ile	Pro ' 2485		Val	Lys	Val	Asp 2490		Lys	Glu
Glu	Pro 2495	Leu	Ala	Val	Ser	Lys 2500	Leu	Thr	Arg	Thr	Ser 2505	Gly	Glu	Thr
Thr	Gln 2510		His	Thr	Glu	Pro 2515	Thr	Gly	Asp	Ser	Lys 2520	Ser	Ile	Lys
	Phe 2525	Lys	Glu	Ser		Lys 2530		Ile			Pro 2535		Ala	Ser
Val	Thr 2540		Ser	Arg	Arg	Gln 2545		Arg	Thr	Arg	Lys 2550		Lys	Ala
Arg	Ala 2555		Glu	Asp	Leu	Val 2560		Phe	Lys	Glu	Leu 2565	Phe	Ser	Ala
Pro	Gly 2570		Thr	Glu	Glu	Ser 2575	Met	Thr	Ile	Asp	Lys 2580	Asn	Thr	Lys
Ile	Pro 2585		Lys	Ser	Pro	Pro 2590		Glu	Leu	Thr	Asp 2595	Thr	Ala	Thr
Ser	Thr 2600		Arg	Cys	Pro	Lys 2605		Arg	Pro	Arg	Lys 2610		Val	Lys

Glu	Glu 2615	Leu	Ser	Ala	Val	Glu 2620	Arg	Leu	rnr		rnr 2625	ser	GТĀ	Gin
Ser	Thr 2630	His	Thr	His		Glu 2635	Pro	Ala	Ser	Gly	Asp 2640	Glu	Gly	Ile
Lys	Val 2645		Lys	Gln		Ala 2650		Lys	Lys	Pro	Asn 2655	Pro	Val	Glu
Glu	Glu 2660		Ser	Arg	Arg	Arg 2665	Pro	Arg	Ala	Pro	Lys 2670	Glu	Lys	Ala
Gln	Pro 2675	Leu	Glu	Asp	Leu	Ala 2680		Phe	Thr		Leu 2685	Ser	Glu	Thr
Ser	Gly 2690		Thr	Gln	<b>Gl</b> u	Ser 2695	Leu	Thr	Ala	Gly	Lys 2700	Ala	Thr	Lys
Ile	Pro 2705	Cys	Glu	Ser		Pro 2710	Leu	Glu	Val		Asp 2715		Thr	Ala
Ser	Thr 2720		Arg	His	Leu	Arg 2725	Thr	Arg	Val		Lys 2730		Gln	Val
Lys	Glu 2735		Pro	Ser	Ala	Val 2740		Phe	Thr	Gln	Thr 2745		Gly	Glu
Thr	Thr 2750		Ala	Asp		Glu 2755		Ala	Gly	Glu	Asp 2760		Gly	Ile
Lys	Ala 2765		Lys	Glu	Ser	Ala 2770		Gln	Thr	Pro	Ala 2775	Pro	Ala	Ala
Ser	Val 2780		Gly	Ser	Arg	Arg 2785		Pro	Arg		Pro 2790	Arg	Glu	Ser
Ala	Gln 2795		Ile	Glu		Leu 2800		Gly	Phe		Asp 2805		Ala	Ala
Gly	His 2810	Thr	Glu	Glu	Ser	Met 2815	Thr	Asp	Asp	Lys	Thr 2820	Thr	Lys	Ile
Pro	Cys 2825		Ser	Ser	Pro	Glu 2830		Glu	Asp	Thr	Ala 2835	Thr	Ser	Ser
Lys	Arg 2840	Arg	Pro	Arg	Thr	Arg 2845	Ala	Gln	Lys	Val	Glu 2850	Val	Lys	Glu
Glu	Leu 2855	Leu	Ala	Val	GТĀ	Lys 2860	Leu	Thr	Gln	Thr	Ser 2865	Gly	Glu	Thr
Thr	His 2870	Thr	Asp	Lys	Glu	Pro 2875	Val	Gly	Glu	Gly	Lys 2880		Thr	Lys
Ala	Phe 2885	Lys	Gln	Pro	Ala	Lys 2890		Asn	Val	Asp	Ala 2895		Asp	Val
Ile	Gly 2900	Ser	Arg	Arg	Gln	Pro 2905	Arg	Ala	Pro	Lys	Glu 2910		Ala	Gln

Pro	Leu 2915	Glu	Asp	Leu	Ala	Ser 2920	Phe	Gln	Glu	Leu	Ser 2925	Gln	Thr	Pro
Gly	His 2930	Thr	Glu	Glu	Leu	Ala 2935	Asn	Gly	Ala		Asp 2940	Ser	Phe	Thr
Ser	Ala 2945	Pro	Lys	Gln	Thr	Pro 2950	Asp	Ser	Gly	Lys	Pro 2955	Leu	Lys	Ile
Ser	Arg 2960	Arg	Val	Leu	Arg	Ala 2965	Pro	Lys	Val	Glu	Pro 2970	Val	Gly	Asp
Val	Val 2975	Ser	Thr	Arg	Asp	Pro 2980	Val	Lys	Ser		Ser 2985	Lys	Ser	Asn
Thr	Ser 2990	Leu	Pro	Pro	Leu	Pro 2995	Phe	Lys	Arg	Gly	Gly 3000	Gly	Lys	Asp
Gly	Ser 3005	Val	Thr	Gly	Thr	Lys 3010		Leu	Arg		Met 3015	Pro	Ala	Pro
Glu	Glu 3020		Val	Glu	Glu	Leu 3025	Pro	Ala	Ser	Lys	Lys 3030	Gln	Arg	Val
Ala	Pro 3035		Ala	Arg	Gly	Lys 3040	Ser	Ser	Glu	Pro	Val 3045	Val	Ile	Met
Lys	Arg 3050		Leu	Arg	Thr	Ser 3055	Ala	Lys	Arg	Ile	Glu 3060	Pro	Ala	Glu
Glu	Leu 3065		Ser	Asn	Asp	Met 3070		Thr	Asn	Lys	Glu 3075	Glu	His	Lys
Leu	Gln 3080	Asp	Ser	Val	Pro	Glu 3085		Lys	Gly	Ile	Ser 3090	Leu	Arg	Ser
Arg	Arg 3095		Asp	Lys	Thr	Glu 3100		Glu	Gln	Gln	Ile 3105	Thr	Glu	Val
Phe	Val 3110	Leu	Ala	Glu	Arg	Ile 3115	Glu	Ile	Asn	Arg	Asn 3120	Glu	Lys	Lys
Pro	Met 3125	Lys	Thr	Ser	Pro	Glu 3130	Met	Asp	Ile	Gln	Asn 3135	Pro	Asp	Asp
Gly	Ala 3140	Arg	Lys	Pro	Ile	Pro 3145	Arg	Asp	Lys	Val	Thr 3150	Glu	Asn	Lys
Arg	Cys 3155		Arg	Ser	Ala	Arg 3160		Asn	Glu	Ser	Ser 3165	Gln	Pro	Lys
Val	Ala 3170	Glu	Glu	Ser	Gly	Gly 3175		Lys	Ser	Ala	Lys 3180		Leu	Met
Gln	Asn 3185	Gln	Lys	Gly	Lys	Gly 3190		Ala	Gly	Asn	Ser 3195	Asp	Ser	Met
Суз	Leu 3200	Arg	Ser	Arg	Lys	Thr 3205	Lys	Ser	Gln		Ala 3210		Ser	Thr
										Pa	ge 33	1		

Leu Glu Ser Lys Ser Val Gln Arg Val Thr Arg Ser Val Lys Arg 3215  $\phantom{\bigg|}$  3220  $\phantom{\bigg|}$  3225

Cys Ala Glu Asn Pro Lys Lys Ala Glu Asp Asn Val Cys Val Lys 3230 3235 3240

Lys Ile Thr Thr Arg Ser His Arg Asp Ser Glu Asp Ile 3245 3250 3255

<210> 200

<211> 47

<212> PRT

<213> Homo sapiens

<400> 200

Asp Leu Asp Pro Asp Asp Arg Glu Glu Gly Ala Ala Ser Thr Ala Glu 20 25 30

Glu Ala Ala Lys Lys Lys Arg Arg Lys Lys Lys Lys Ser Lys Gly Pro  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Ser Ala Ala Gly Glu Gln Glu Pro Asp Lys Glu Ser Gly Ala Ser Val $50 \\ 0 \\ 0 \\ 0$ 

Asp Glu Val Ala Arg Gln Leu Glu Arg Ser Ala Leu Glu Asp Lys Glu 65 70 75 80

Arg Asp Glu Asp Asp Glu Asp Gly Asp Gly Asp Gly Asp Gly Ala Thr 85 90 95

Gly Lys Lys Lys Lys Lys Lys Lys Lys Lys Arg Gly Pro Lys Val Gln 100 105 110

Thr Asp Pro Pro Ser Val Pro Ile Cys Asp Leu Tyr Pro Asn Gly Val 115 125 125

Phe Pro Lys Gly Gln Glu Cys Glu Tyr Pro Pro Thr Gln Asp Gly Arg 130 135 140

Thr Ala Ala Trp Arg Thr Thr Ser Glu Glu Lys Lys Ala Leu Asp Gln 145  $\phantom{\bigg|}$  150  $\phantom{\bigg|}$  155  $\phantom{\bigg|}$  160

Ala Ser Glu Glu Ile Trp Asn Asp Phe Arg Glu Ala Ala Glu Ala His 165 170 175

Arg Gln Val Arg Lys Tyr Val Met Ser Trp Ile Lys Pro Gly Met Thr 180  $$185\$ 

Met Ile Glu Ile Cys Glu Lys Leu Glu Asp Cys Ser Arg Lys Leu Ile 195 200 . 205

Lys Glu Asn Gly Leu Asn Ala Gly Leu Ala Phe Pro Thr Gly Cys Ser 210 225 220

Leu Asn Asn Cys Ala Ala His Tyr Thr Pro Asn Ala Gly Asp Thr Thr 225 230 235 240

Val Leu Gln Tyr Asp Asp Ile Cys Lys Ile Asp Phe Gly Thr His Ile 245 250 250

Ser Gly Arg Ile Ile Asp Cys Ala Phe Thr Val Thr Phe Asn Pro Lys  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$ 

Tyr Asp Thr Leu Leu Lys Ala Val Lys Asp Ala Thr Asn Thr Gly Ile 275 280 285

Lys Cys Ala Gly Ile Asp Val Arg Leu Cys Asp Val Gly Glu Ala Ile 290 295 300

Gln Glu Val Met Glu Ser Tyr Glu Val Glu Ile Asp Gly Lys Thr Tyr 305 310 315 320

Gln Val Lys Pro Ile Arg Asn Leu Asn Gly His Ser Ile Gly Gln Tyr \$325\$

Arg Ile His Ala Gly Lys Thr Val Pro Ile Val Lys Gly Glu Ala 340 345 350

Thr Arg Met Glu Glu Gly Glu Val Tyr Ala Ile Glu Thr Phe Gly Ser 355 360 365

Thr Gly Lys Gly Val Val His Asp Asp Met Glu Cys Ser His Tyr Met 370 375 380

Lys Asn Phe Asp Val Gly His Val Pro Ile Arg Leu Pro Arg Thr Lys 385 390 395 400

His Leu Leu Asn Val Ile Asn Glu Asn Phe Gly Thr Leu Ala Phe Cys 405 410 415

Arg Arg Trp Leu Asp Arg Leu Gly Glu Ser Lys Tyr Leu Met Ala Leu 420 425 430

Lys Asn Leu Cys Asp Leu Gly Ile Val Asp Pro Tyr Pro Pro Leu Cys 435 440 445

Asp Ile Lys Gly Ser Tyr Thr Ala Gln Phe Glu His Thr Ile Leu Leu 450 455 460

Arg Pro Thr Cys Lys Glu Val Val Ser Arg Gly Asp Asp Tyr 465 470 475

<210> 201

<211> 488

<212> PRT <213> Homo sapiens

<400> 201

Met His Gly Arg Lys Asp Asp Ala Gln Lys Gln Pro Val Lys Asn Gln l 10 15

Leu Gly Leu Asn Pro Gln Ser His Leu Pro Glu Leu Gln Leu Phe Gln 20 25 30

Ala Glu Gly Lys Ile Tyr Lys Tyr Asp His Met Glu Lys Ser Val Asn 35 40 45

Ser Ser Ser Leu Val Ser Pro Pro Gln Arg Ile Ser Ser Thr Val Lys 50 60 Thr His Ile Ser His Ile Tyr Glu Cys Asn Phe Val Asp Ser Leu Phe 65 70 75 80 Thr Gln Lys Glu Lys Ala Asn Ile Gly Thr Glu His Tyr Lys Cys Asn 85 90 95 Glu Arg Gly Lys Ala Phe His Gln Gly Leu His Phe Thr Ile His Gln 100 105 110 Ile Ile His Thr Lys Glu Thr Gln Phe Lys Cys Asp Ile Cys Gly Lys 115 120 125Ile Phe Asn Lys Lys Ser Asn Leu Ala Ser His Gln Arg Ile His Thr 130 135 140Gly Glu Lys Pro Tyr Lys Cys Asn Glu Cys Gly Lys Val Phe His Asn 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$ Met Ser His Leu Ala Gln His Arg Arg Ile His Thr Gly Glu Lys Pro 165 170 175Tyr Lys Cys Asn Glu Cys Gly Lys Val Phe Asn Gln Ile Ser His Leu 180  $$185\$ Ala Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Lys Cys Asn 195 200 205Glu Cys Gly Lys Val Phe His Gln Ile Ser His Leu Ala Gln His Arg 210 215 220Thr Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Asn Lys Cys Gly Lys 225 230 235 240 Val Phe Ser Arg Asn Ser Tyr Leu Val Gln His Leu Ile Ile His Thr 245 250 255Gly Glu Lys Pro Tyr Arg Cys Asn Val Cys Gly Lys Val Phe Ser His 260 265 270Lys Ser Ser Leu Val Asn His Trp Arg Ile His Thr Gly Glu Lys Pro 275 280 285 Tyr Lys Cys Asn Glu Cys Gly Lys Val Phe Ser His Lys Ser Ser Leu 290 295 300 Val Asn His Trp Arg Ile His Thr Gly Glu Lys Pro Tyr Lys Cys Asn 305 310 315 320Ile Ile His Ala Gly Glu Lys Pro Tyr Lys Cys Asp Glu Cys Asp Lys 340 345 350Ala Phe Ser Gln Asn Ser His Leu Val Gln His His Arg Ile His Thr

Page 334

ەد 355

Gly Glu Lys Pro Tyr Lys Cys Asp Glu Cys Gly Lys Val Phe Ser Gln 370 375 380

Asn Ser Tyr Leu Ala Tyr His Trp Arg Ile His Thr Gly Glu Lys Ala 385 390 395 400

Tyr Lys Cys Asn Glu Cys Gly Lys Val Phe Gly Leu Asn Ser Ser Leu  $405 \hspace{1.5cm} 410 \hspace{1.5cm} 415 \hspace{1.5cm}$ 

Ala His His Arg Lys Ile His Thr Gly Glu Lys Pro Phe Lys Cys Asn 420 425 430

Glu Cys Gly Lys Ala Phe Ser Met Arg Ser Ser Leu Thr Asn His His 435 440 445

Ala Ile His Thr Gly Glu Lys His Phe Lys Cys Asn Glu Cys Gly Lys 450 455 460

Leu Phe Arg Asp Asn Ser Tyr Leu Val Arg His Gln Arg Phe His Ala 465 470 475 480

Gly Lys Lys Ser Asn Thr Cys Asn 485

<210> 202

(211> 553

<212> PRT

<213> Homo sapiens

<400> 202

Met Leu Ser Val Arg Val Ala Ala Ala Val Val Arg Ala Leu Pro Arg 1 5 10 15

Arg Ala Gly Leu Val Ser Arg Asn Ala Leu Gly Ser Ser Phe Ile Ala  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$ 

Ala Arg Asn Phe His Ala Ser Asn Thr His Leu Gln Lys Thr Gly Thr 35  $\phantom{\bigg|}40\phantom{\bigg|}$ 

Ala Glu Met Ser Ser Ile Leu Glu Glu Arg Ile Leu Gly Ala Asp Thr 50 60

Ser Val Asp Leu Glu Glu Thr Gly Arg Val Leu Ser Ile Gly Asp Gly 65 70 75 80

Ile Ala Arg Val His Gly Leu Arg Asn Val Gln Ala Glu Glu Met Val 85 90 95

Glu Phe Ser Ser Gly Leu Lys Gly Met Ser Leu Asn Leu Glu Pro Asp 100 105 110

Asn Val Gly Val Val Val Phe Gly Asn Asp Lys Leu Ile Lys Glu Gly 115 120 125

Asp Ile Val Lys Arg Thr Gly Ala Ile Val Asp Val Pro Val Gly Glu 130  $$135\$ 

Glu Leu Leu Gly Arg Val Val Asp Ala Leu Gly Asn Ala Ile Asp Gly

145 150 100

Lys Gly Pro Ile Gly Ser Lys Thr Arg Arg Arg Val Gly Leu Lys Ala 165 170 175

Pro Gly Ile Ile Pro Arg Ile Ser Val Arg Glu Pro Met Gln Thr Gly 180 185 190

Ile Lys Ala Val Asp Ser Leu Val Pro Ile Gly Arg Gly Gln Arg Glu 195 200 205

Leu Ile Ile Gly Asp Arg Gln Thr Gly Lys Thr Ser Ile Ala Ile Asp 210 215 220

Thr Ile Ile Asn Gln Lys Arg Phe Asn Asp Gly Ser Asp Glu Lys Lys 225 230 230 235

Lys Leu Tyr Cys Ile Tyr Val Ala Ile Gly Gln Lys Arg Ser Thr Val 245 250 255

Ala Gln Leu Val Lys Arg Leu Thr Asp Ala Asp Ala Met Lys Tyr Thr 260 265 270

Ile Val Val Ser Ala Thr Ala Ser Asp Ala Ala Pro Leu Gln Tyr Leu 275 280 285

Ala Pro Tyr Ser Gly Cys Ser Met Gly Glu Tyr Phe Arg Asp Asn Gly 290 295 300

Lys His Ala Leu Ile Ile Tyr Asp Asp Leu Ser Lys Gln Ala Val Ala 305 310 315 320

Tyr Arg Gln Met Ser Leu Leu Leu Arg Arg Pro Pro Gly Arg Glu Ala 325 330 335

Tyr Pro Gly Asp Val Phe Tyr Leu His Ser Arg Leu Leu Glu Arg Ala  $340 \hspace{1.5cm} 345 \hspace{1.5cm} 350$ 

Ala Lys Met Asn Asp Ala Phe Gly Gly Gly Ser Leu Thr Ala Leu Pro 355 360 365

Val Ile Glu Thr Gln Ala Gly Asp Val Ser Ala Tyr Ile Pro Thr Asn 370 375 380

Val Ile Ser Ile Thr Asp Gly Gln Ile Phe Leu Glu Thr Glu Leu Phe 385  $\phantom{\bigg|}390\phantom{\bigg|}395\phantom{\bigg|}400\phantom{\bigg|}$ 

Tyr Lys Gly Ile Arg Pro Ala Ile Asn Val Gly Leu Ser Val Ser Arg 405 410 415

Val Gly Ser Ala Ala Gln Thr Arg Ala Met Lys Gln Val Ala Gly Thr  $420 \hspace{1.5cm} 425 \hspace{1.5cm} 430$ 

Met Lys Leu Glu Leu Ala Gln Tyr Arg Glu Val Ala Ala Phe Ala Gln 435 440 445

Phe Gly Ser Asp Leu Asp Ala Ala Thr Gln Gln Leu Leu Ser Arg Gly 450 455 460

Val Arg Leu Thr Glu Leu Leu Lys Gln Giy Gin Tyr Ser Pro Met Ala 465 470 475 480

Ile Glu Glu Gln Val Ala Val Ile Tyr Ala Gly Val Arg Gly Tyr Leu 485 490 495

Asp Lys Leu Glu Pro Ser Lys Ile Thr Lys Phe Glu Asn Ala Phe Leu 500 505 510

Ser His Val Val Ser Gln His Gln Ala Leu Leu Gly Thr Ile Arg Ala 515 520 525

Asp Gly Lys Ile Ser Glu Gln Ser Asp Ala Lys Leu Lys Glu Ile Val 530 535 540

Thr Asn Phe Leu Ala Gly Phe Glu Ala 545 550

<210> 203

<211> 46

<213> Homo sapiens

<400> 203

Asp Ser Gly Lys Ser Thr Thr Thr Gly His Leu Ile Tyr Lys Cys Gly  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Gly Ile Asp Lys Arg Thr Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu 35 40 45

Met Gly Lys Gly Ser Phe Lys Tyr Ala Trp Val Leu Asp Lys Leu Lys 50 60

Ala Glu Arg Glu Arg Gly Ile Thr Ile Asp Ile Ser Leu Trp Lys Phe 65 70 75 80

Glu Thr Ser Lys Tyr Tyr Val Thr Ile Ile Asp Ala Pro Gly His Arg  $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Asp Phe Ile Lys Asn Met Ile Thr Gly Thr Ser Gln Ala Asp Cys Ala  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105$ 

Val Leu Ile Val Ala Ala Gly Val Gly Glu Phe Glu Ala Gly Ile Ser 115 120 125

Lys Asn Gly Gln Thr Arg Glu His Ala Leu Leu Ala Tyr Thr Leu Gly 130 135 140

Val Lys Gln Leu Ile Val Gly Val Asn Lys Met Asp Ser Thr Glu Pro 145 150 150 160

Pro Tyr Ser Gln Lys Arg Tyr Glu Glu Ile Val Lys Glu Val Ser Thr 165 170 175

Tyr Ile Lys Lys Ile Gly Tyr Asn Pro Asp Thr Val Ala Phe Val Pro 185 185

Ile Ser Gly Trp Asn Gly Asp Asn Met Leu Glu Fro Ser Ala Ash Met 195 200 205

Pro Trp Phe Lys Gly Trp Lys Val Thr Arg Lys Asp Gly Asn Ala Ser 210 215 220

Gly Thr Thr Leu Leu Glu Ala Val Asp Cys Ile Leu Pro Pro Thr Arg 225 230 235 240

Pro Thr Asp Lys Pro Leu Arg Leu Pro Leu Gln Asp Val Tyr Lys Ile 245 250 255

Gly Gly Ile Gly Thr Val Pro Val Gly Arg Val Glu Thr Gly Val Leu  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 261 \hspace{1.5cm} 270 \hspace{1.5cm}$ 

Val Lys Ser Val Glu Met His His Glu Ala Leu Ser Glu Ala Leu Pro 290 300

Gly Asp Asn Val Gly Phe Asn Val Lys Asn Val Ser Val Lys Asp Val 305 310 315 320

Arg Arg Gly Asn Val Ala Gly Asp Ser Lys Asn Asp Pro Pro Met Glu 325 . 330 335

Ile Ser Ala Gly Tyr Ala Pro Val Leu Asp Cys His Thr Ala His Ile 355  $\phantom{\bigg|}360\phantom{\bigg|}$ 

Ala Cys Lys Phe Ala Glu Leu Lys Glu Lys Ile Asp Arg Arg Ser Gly 370 375 380

Lys Lys Leu Glu Asp Gly Pro Lys Phe Leu Lys Ser Gly Asp Ala Ala 385 390 395 400

Ile Val Asp Met Val Pro Gly Lys Pro Met Cys Val Glu Ser Phe Ser 415

Asp Tyr Pro Pro Leu Gly Arg Phe Ala Val Arg Asp Met Arg Gln Thr  $420 \hspace{1.5cm} 425 \hspace{1.5cm} 430$ 

Val Ala Val Gly Val Ile Lys Ala Val Asp Lys Lys Ala Ala Gly Ala 435  $\phantom{-}440\phantom{0}$  445

Gly Lys Val Thr Lys Ser Ala Gln Lys Ala Gln Lys Ala Lys 450 460

<210> 204 <211> 1069 <212> PRT

<213> Homo sapiens

<400> 204

Met Leu Arg Met Arg Thr Ala Gly Trp Ala Arg Gly Trp Cys Leu Gly
1 5 10 15

Cys Cys Leu Leu Leu Pro Leu Ser Phe Ser Leu Ala Ala Ala Lys Gin 20 25 30

Leu Leu Arg Tyr Arg Leu Ala Glu Glu Gly Pro Ala Asp Val Arg Ile  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Gly Asn Val Ala Ser Asp Leu Gly Ile Val Thr Gly Ser Gly Glu Val 50  $\,$ 

Thr Phe Ser Leu Glu Ser Gly Ser Glu Tyr Leu Lys Ile Asp Asn Leu 65 70 75 80

Thr Gly Glu Leu Ser Thr Ser Glu Arg Arg Ile Asp Arg Glu Lys Leu 85 90 95

Pro Gln Cys Gln Met Ile Phe Asp Glu Asn Glu Cys Phe Leu Asp Phe 100  $\phantom{-}105\phantom{0}$  105

Glu Val Ser Val Ile Gly Pro Ser Gln Ser Trp Val Asp Leu Phe Glu 115 120 125

Gly Gln Val Ile Val Leu Asp Ile Asn Asp Asn Thr Pro Thr Phe Pro 130 135 140

Ser Pro Val Leu Thr Leu Thr Val Glu Glu Asn Arg Pro Val Gly Thr 145 150 155 160

Leu Tyr Leu Leu Pro Thr Ala Thr Asp Arg Asp Phe Gly Arg Asn Gly 165 170 175

Ile Glu Arg Tyr Glu Leu Leu Gln Glu Pro Gly Gly Gly Ser Gly 180 185 190

Gly Glu Ser Arg Arg Ala Gly Ala Ala Asp Ser Ala Pro Tyr Pro Gly 195 200 205

Gly Gly Gly Asn Gly Ala Ser Gly Gly Gly Ser Gly Gly Ser Lys Arg 210 215 220

Arg Leu Asp Ala Ser Glu Gly Gly Gly Gly Thr Asn Pro Gly Gly Arg 225 230 235 240

Ser Ser Val Phe Glu Leu Gln Val Ala Asp Thr Pro Asp Gly Glu Lys 245 250 255

Gln Pro Gln Leu Ile Val Lys Gly Ala Leu Asp Arg Glu Gln Arg Asp 260 265 270

Ser Tyr Glu Leu Thr Leu Arg Val Arg Asp Gly Gly Asp Pro Pro Arg 275 280 285

Ser Ser Gln Ala Ile Leu Arg Val Leu Ile Thr Asp Val Asn Asp Asn 290 295 300

Ser Pro Arg Phe Glu Lys Ser Val Tyr Glu Ala Asp Leu Ala Glu Asn 305 310 315 320

Ser Ala Pro Gly Thr Pro Ile Leu Gln Leu Arg Ala Ala Asp Leu Asp 325 330 335

Val Gly Val Asn Gly Gln Ile Glu Tyr Val Phe Gly Ala Ala Thr Glu 340 345 350Ser Val Arg Arg Leu Leu Arg Leu Asp Glu Thr Ser Gly Trp Leu Ser 355 360 365Val Leu His Arg Ile Asp Arg Glu Glu Val Asn Gln Leu Arg Phe Thr 370 380Val Met Ala Arg Asp Arg Gly Gln Pro Pro Lys Thr Asp Lys Ala Thr 385 390 395 400 Val Val Leu Asn Ile Lys Asp Glu Asn Asp Asn Val Pro Ser Ile Glu 405 410 415Ile Arg Lys Ile Gly Arg Ile Pro Leu Lys Asp Gly Val Ala Asn Val 420 425 430 Ala Glu Asp Val Leu Val Asp Thr Pro Ile Ala Leu Val Gln Val Ser 435 440 445 Asp Arg Asp Gln Gly Glu Asn Gly Val Val Thr Cys Thr Val Val Gly 450 460 Asp Val Pro Phe Gln Leu Lys Pro Ala Ser Asp Thr Glu Gly Asp Gln 465 470 475 480 Ala Thr Arg Glu Phe Asn Val Val Ile Val Ala Val Asp Ser Gly Ser 500 505 510 Pro Ser Leu Ser Ser Lys Asn Ser Leu Ile Val Lys Val Gly Asp Thr 515 520 525Asn Asp Asn Pro Pro Met Phe Gly Gln Ser Val Val Glu Val Tyr Phe 530 535 540 Pro Glu Asn Asn Ile Pro Gly Glu Arg Val Ala Thr Val Leu Ala Thr 545 550 555 560Asp Ala Asp Ser Gly Lys Asn Ala Glu Ile Ala Tyr Ser Leu Asp Ser 565 570 575 Ser Val Met Gly Ile Phe Ala Ile Asp Pro Asp Ser Gly Asp Ile Leu 580 585 590Val Asn Thr Val Leu Asp Arg Glu Gln Thr Asp Arg Tyr Glu Phe Lys 595 600 605

Val Ile Val Gln Val Ala Asp Lys Asn Asp Asn Asp Pro Lys Phe Met 625 630 635 635

Val Asn Ala Lys Asp Lys Gly Ile Pro Val Leu Gln Gly Ser Thr Thr 610 620

Gln Asp Val Phe Thr Phe Tyr Val Lys Glu Asn Leu Gln Pro Asn Ser 645 650 655

Pro Val Gly Met Val Thr Val Met Asp Ala Asp Lys Gly Arg Asn Ala 660 665 670 • Glu Met Ser Leu Tyr Ile Glu Glu Asn Asn Asn Ile Phe Ser Ile Glu 675 680 685Asn Asp Thr Gly Thr Ile Tyr Ser Thr Met Ser Phe Asp Arg Glu His Gln Thr Thr Tyr Thr Phe Arg Val Lys Ala Val Asp Gly Gly Asp Pro 705 710 715 720 Pro Arg Ser Ala Thr Ala Thr Val Ser Leu Phe Val Met Asp Glu Asn 725 730 735 Asp Asn Ala Pro Thr Val Thr Leu Pro Lys Asn Ile Ser Tyr Thr Leu 740 745 750Leu Pro Pro Ser Ser Asn Val Arg Thr Val Val Ala Thr Val Leu Ala 755 760 765Thr Asp Ser Asp Asp Gly Ile Asn Ala Asp Leu Asn Tyr Ser Ile Val Gly Gly Asn Pro Phe Lys Leu Phe Glu Ile Asp Pro Thr Ser Gly Val 785 790 795 800 Val Ser Leu Val Gly Lys Leu Thr Gln Lys His Tyr Gly Leu His Arg 805 810 815 Leu Val Val Gln Val Asn Asp Ser Gly Gln Pro Ser Gln Ser Thr Thr 820 825 830 Thr Val Val His Val Phe Val Asn Glu Ser Val Ser Asn Ala Thr Ala 835 840 845 Ile Ala Gly Asp Pro Ser Tyr Glu Ile Ser Lys Gln Arg Leu Ser Ile 865 870 875 880 Val Ile Gly Val Val Ala Gly Ile Met Thr Val Ile Leu Ile Ile Leu 885  $890\,$  895 Ile Val Val Met Ala Arg Tyr Cys Arg Ser Lys Asn Lys Asn Gly Tyr 900 905 910 Glu Ala Gly Lys Lys Asp His Glu Asp Phe Phe Thr Pro Gln Gln His 915 920 925 Asp Lys Ser Lys Lys Pro Lys Lys Asp Lys Lys Asn Lys Lys Ser Lys 930 935 940 Gln Pro Leu Tyr Ser Ser Ile Val Thr Val Glu Ala Ser Lys Pro Asn 945 950 950 955 Gly Gln Arg Tyr Asp Ser Val Asn Glu Lys Leu Ser Asp Ser Pro Ser-

Page 341

סוע טוע

Met Gly Arg Tyr Arg Ser Val Asn Gly Gly Pro Gly Ser Pro Asp Leu 980 985 990

Ala Arg His Tyr Lys Ser Ser Ser Pro Leu Pro Thr Val Gln Leu His 995 1000 1005

Pro Gln Ser Pro Thr Ala Gly Lys Lys His Gln Ala Val Gln Asp 1010 1015 1020

Leu Pro Pro Ala Asn Thr Phe Val Gly Ala Gly Asp Asn Ile Ser  $\cdot$  1025  $\cdot$  1030  $\cdot$  1035

Ile Gly Ser Asp His Cys Ser Glu Tyr Ser Cys Gln Thr Asn Asn 1040 1045 1050

Lys Tyr Ser Lys Gln Met Arg Leu His Pro Tyr Ile Thr Val Phe 1055  $\phantom{\bigg|}$  1060  $\phantom{\bigg|}$  1065

Gly

<210> 205

<211> 401

<212> PRT

<213> Homo sapiens

<400> 205

Met Ser Phe Ser Lys Thr His Ser Thr Ala Thr Met Pro Pro Pro Ile 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Asn Pro Ile Leu Ala Ser Leu Gln His Asn Ser Ile Leu Thr Pro Thr  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Arg Val Ser Ser Ser Ala Thr Lys Gln Lys Val Leu Ser Pro Pro His  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Ile Lys Ala Asp Phe Asn Leu Ala Asp Phe Glu Cys Glu Glu Asp Pro  $50 \hspace{1cm} 60$ 

Phe Asp Asn Leu Glu Leu Lys Thr Ile Asp Glu Lys Glu Glu Leu Arg 65 70 75 80

Asn Ile Leu Val Gly Thr Thr Gly Pro Ile Met Ala Gln Leu Leu Asp 85 90 95

Asn Asn Leu Pro Arg Gly Gly Ser Gly Ser Val Leu Gln Asp Glu Glu 100 105 110

Val Leu Ala Ser Leu Glu Arg Ala Thr Leu Asp Phe Lys Pro Leu His 115 120 125

Lys Pro Asn Gly Phe Ile Thr Leu Pro Gln Leu Gly Asn Cys Glu Lys 130 135 140

Met Ser Leu Ser Ser Lys Val Ser Leu Pro Pro Ile Pro Ala Val Ser 145 150 160

Asn Ile Lys Ser Leu Ser Phe Pro Lys Leu Asp Ser Asp Ser Asn

165 1/0 1/3

Gln Lys Thr Ala Lys Leu Ala Ser Thr Phe His Ser Thr Ser Cys Leu 180 195 190

Arg Asn Gly Thr Phe Gln Asn Ser Leu Lys Pro Ser Thr Gln Ser Ser 195 200 205

Ala Ser Glu Leu Asn Gly His His Thr Leu Gly Leu Ser Ala Leu Asn 210 215 220

Leu Asp Ser Gly Thr Glu Met Pro Ala Leu Thr Ser Ser Gln Met Pro 225 230 240

Ser Leu Ser Val Leu Ser Val Cys Thr Glu Glu Ser Ser Pro Pro Asn 245 250 255

Thr Gly Pro Thr Val Thr Pro Pro Asn Phe Ser Val Ser Gln Val Pro 260 265 270

Asn Met Pro Ser Cys Pro Gln Ala Tyr Ser Glu Leu Gln Met Leu Ser 275 280 285

Pro Ser Glu Arg Gln Cys Val Glu Thr Val Val Asn Met Gly Tyr Ser 290 300

Tyr Glu Cys Val Leu Arg Ala Met Lys Lys Lys Gly Glu Asn Ile Glu 305  $\phantom{\bigg|}310\phantom{\bigg|}310\phantom{\bigg|}315\phantom{\bigg|}$ 

Gln Ile Leu Asp Tyr Leu Phe Ala His Gly Gln Leu Cys Glu Lys Gly 325 330 335

Phe Asp Pro Leu Leu Val Glu Glu Ala Leu Glu Met His Gln Cys Ser 340 345 350

Glu Glu Lys Met Met Glu Phe Leu Gln Leu Met Ser Lys Phe Lys Glu 355 360 365

Met Gly Phe Glu Leu Lys Asp Ile Lys Glu Val Leu Leu His Asn 370 375 380

Asn Asp Gln Asp Asn Ala Leu Glu Asp Leu Met Ala Arg Ala Gly Ala 385 390 395 400

Ser

<210> 206

<211> 285

<212> PRT

<213> Homo sapiens

<400> 206

Met Glu Val Pro Pro Pro Asp Ala Gly Ser Phe Leu Cys Arg Ala Leu 1 5 10 15

Cys Leu Phe Pro Arg Val Phe Ala Ala Glu Ala Val Thr Ala Asp Ser  $20 \hspace{1cm} 25 \hspace{1cm} 30$ 

Glu Val Leu Glu Glu Arg Gln Lys Arg Leu Pro Tyr Val Pro Glu Pro

35 40 45

Tyr Tyr Pro Glu Ser Gly Trp Asp Arg Leu Arg Glu Leu Phe Gly Lys 50 . 55 60

Asp Glu Gln Gln Arg Ile Ser Lys Asp Leu Ala Asn Ile Cys Lys Thr 65 70 75  $\cdot$  80

Ala Ala Thr Ala Gly Ile Ile Gly Trp Val Tyr Gly Gly Ile Pro Ala  $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Phe Ile His Ala Lys Gln Gln Tyr Ile Glu Gln Ser Gln Ala Glu Ile 100 \$105\$

Tyr His Asn Arg Phe Asp Ala Val Gln Ser Ala His Arg Ala Ala Thr 115 120 125

Phe Val Thr Ile Phe Asn Thr Val Asn Thr Ser Leu Asn Val Tyr Arg 145 150 155 160

Asn Lys Asp Ala Leu Ser His Phe Val Ile Ala Gly Ala Val Thr Gly 165 170 175

Ser Leu Phe Arg Ile Asn Val Gly Leu Arg Gly Leu Val Ala Gly Gly 180 185 190

Ile Ile Gly Ala Leu Leu Gly Thr Pro Val Gly Gly Leu Leu Met Ala 195  $\phantom{\bigg|}200\phantom{\bigg|}205\phantom{\bigg|}$ 

Phe Gln Lys Tyr Ser Gly Glu Thr Val Gln Glu Arg Lys Gln Lys Asp 210 220

Arg Lys Ala Leu His Glu Leu Lys Leu Glu Glu Trp Lys Gly Arg Leu 225 230 235 240

Gln Val Thr Glu His Leu Pro Glu Lys Ile Glu Ser Ser Leu Gln Glu 245  $\phantom{\bigg|}250\phantom{\bigg|}250\phantom{\bigg|}$ 

Asp Glu Pro Glu Asn Asp Ala Lys Lys Ile Glu Ala Leu Leu Asn Leu 260 265 270

Pro Arg Asn Pro Ser Val Ile Asp Lys Gln Asp Lys Asp 275 280 280

<210> 207

211> 212

<212> PRT

<213> Homo sapiens

<400> 207

Met Leu Asn Lys Val Leu Ser Arg Leu Gly Val Ala Gly Gln Trp Arg 1 5 10 15

Ala Pro Ala Cys Ala Leu Leu Leu Phe Pro Leu Thr Ala Gln His

35 40 45

Glu Asn Phe Arg Lys Lys Gln Ile Glu Glu Leu Lys Gly Gln Glu Val 50 55 60

Ser Pro Lys Val Tyr Phe Met Lys Gln Thr Ile Gly Asn Ser Cys Gly 65 70 75 80

Thr Ile Gly Leu Ile His Ala Val Ala Asn Asn Gln Asp Lys Leu Gly 85 90 95

Phe Glu Asp Gly Ser Val Leu Lys Gln Phe Leu Ser Glu Thr Glu Lys

Met Ser Pro Glu Asp Arg Ala Lys Cys Phe Glu Lys Asn Glu Ala Ile 115 120 125

Gln Ala Ala His Asp Ala Val Ala Gln Glu Gly Gln Cys Arg Val Asp 130 135 140

Asp Lys Val Asn Phe His Phe Ile Leu Phe Asn Asn Val Asp Gly His 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}160\phantom{\bigg|}$ 

Leu Tyr Glu Leu Asp Gly Arg Met Pro Phe Pro Val Asn His Gly Ala 165 170 175

Ser Ser Glu Asp Thr Leu Leu Lys Asp Ala Ala Lys Val Cys Arg Glu 180 185 190

Phe Thr Glu Arg Glu Gln Gly Glu Val Arg Phe Ser Ala Val Ala Leu 195 200 205

Cys Lys Ala Ala 210

<210> 208

211> 596

<212> PRT

<213> Homo sapiens

<400> 208

Met Ser Leu Ser Met Arg Asp Pro Val Ile Pro Gly Thr Ser Met Ala 1  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Tyr His Pro Phe Leu Pro His Arg Ala Pro Asp Phe Ala Met Ser Ala 20 25 30

Val Leu Gly His Gln Pro Pro Phe Phe Pro Ala Leu Thr Leu Pro Pro 35 40 45

Asn Gly Ala Ala Ala Leu Ser Leu Pro Gly Ala Leu Ala Lys Pro Ile 50 60

Met Asp Gln Leu Val Gly Ala Ala Glu Thr Gly Ile Pro Phe Ser Ser 65 70 75 80

Leu Gly Pro Gln Ala His Leu Arg Pro Leu Lys Thr Met Glu Pro Glu 95

Glu Glu Val Glu Asp Asp Pro Lys Val His Leu Glu Ala Lys Glu Leu

100 105 110

Trp Asp Gln Phe His Lys Arg Gly Thr Glu Met Val Ile Thr Lys Ser 115 120 125

Gly Arg Arg Met Phe Pro Pro Phe Lys Val Arg Cys Ser Gly Leu Asp 130 135 140

Lys Lys Ala Lys Tyr Ile Leu Leu Met Asp Ile Ile Ala Ala Asp Asp 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}160\phantom{\bigg|}$ 

Cys Arg Tyr Lys Phe His Asn Ser Arg Trp Met Val Ala Gly Lys Ala 165 170 175

Asp Pro Glu Met Pro Lys Arg Met Tyr Ile His Pro Asp Ser Pro Ala 180 185 190

Thr Gly Glu Gln Trp Met Ser Lys Val Val Thr Phe His Lys Leu Lys 195 200 205

Leu Thr Asn Asn Ile Ser Asp Lys His Gly Phe Thr Leu Ala Phe Pro 210 220

Ser Asp His Ala Thr Trp Gln Gly Asn Tyr Ser Phe Gly Thr Gln Thr 225 230 240

Ile Leu Asn Ser Met His Lys Tyr Gln Pro Arg Phe His Ile Val Arg 245  $\phantom{\bigg|}250\phantom{\bigg|}$ 

Ala Asn Asp Ile Leu Lys Leu Pro Tyr Ser Thr Phe Arg Thr Tyr Leu 260 265 270

Phe Pro Glu Thr Glu Phe Ile Ala Val Thr Ala Tyr Gln Asn Asp Lys  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285$ 

Ile Thr Gln Leu Lys Ile Asp Asn Asn Pro Phe Ala Lys Gly Phe Arg 290 295 300

Asp Thr Gly Asn Gly Arg Arg Glu Lys Arg Gln Gln Leu Thr Leu Gln 305 310 315 320

Ser Met Arg Val Phe Asp Glu Arg His Lys Lys Glu Asn Gly Thr Ser 325 330 335

Asp Glu Ser Ser Ser Glu Gln Ala Ala Phe Asn Cys Phe Ala Gln Ala 340 345 350

Ser Ser Pro Ala Ala Ser Thr Val Gly Thr Ser Asn Leu Lys Asp Leu 355  $\phantom{\bigg|}360\phantom{\bigg|}$  365 .

Cys Pro Ser Glu Gly Glu Ser Asp Ala Glu Ala Glu Ser Lys Glu Glu 370 380

His Gly Pro Glu Ala Cys Asp Ala Ala Lys Ile Ser Thr Thr Ser 385 390 400

Glu Glu Pro Cys Arg Asp Lys Gly Ser Pro Ala Val Lys Ala His Leu 405 410 415

Phe Ala Ala Glu Arg Pro Arg Asp Ser Gly Arg Leu Asp Lys Ala Ser 420 425 430

Pro Asp Ser Arg His Ser Pro Ala Thr Ile Ser Ser Ser Thr Arg Gly 435  $\phantom{-}440\phantom{+}445\phantom{+}$ 

Leu Gly Ala Glu Glu Arg Arg Ser Pro Val Arg Glu Gly Thr Ala Pro 450 460

Ala Lys Val Glu Glu Ala Arg Ala Leu Pro Gly Lys Glu Ala Phe Ala 465 470 475 480

Pro Leu Thr Val Gln Thr Asp Ala Ala Arg Ser Ser Val His Arg His 485 490 495

Pro Phe Arg Asn Leu Asn Thr Met Arg Pro Arg Leu Arg Tyr Ser Pro 500 505 510

Tyr Ser Ile Pro Val Pro Val Pro Asp Gly Ser Ser Leu Leu Thr Thr 515 520 525

Ala Leu Ala Ala Ser Pro Ala Ser Val Ala Val Asp Ser Gly Ser Glu 530 540

Leu Asn Ser Arg Ser Ser Thr Leu Ser Ser Ser Ser Met Ser Leu Ser 545 550 555 560

Pro Lys Leu Cys Ala Glu Lys Glu Ala Ala Thr Ser Glu Leu Gln Ser  $565 \hspace{1.5cm} 570 \hspace{1.5cm} 575$ 

Ile Gln Arg Leu Val Ser Gly Leu Glu Ala Lys Pro Asp Arg Ser Arg 580 585 590

Ser Ala Ser Pro 595

<210> 209

211> 215 212> PRT

<213> Homo sapiens

<400> 209

Met Gly Lys Gly Asp Pro Lys Lys Pro Arg Gly Lys Met Ser Ser Tyr 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Ala Phe Phe Val Gln Thr Cys Arg Glu Glu His Lys Lys Lys His Pro  $20 \hspace{1cm} 25 \hspace{1cm} 30 \hspace{1cm} .$ 

Asp Ala Ser Val Asn Phe Ser Glu Phe Ser Lys Lys Cys Ser Glu Arg 35 40 45

Trp Lys Thr Met Ser Ala Lys Glu Lys Gly Lys Phe Glu Asp Met Ala 50 60

Lys Ala Asp Lys Ala Arg Tyr Glu Arg Glu Met Lys Thr Tyr Ile Pro 65 70 75 80

Pro Lys Gly Glu Thr Lys Lys Lys Phe Lys Asp Pro Asn Ala Pro Lys 85 90 95

Arg Pro Pro Ser Ala Phe Phe Leu Phe Cys Ser Glu Tyr Arg Pro Lys 100 105 110

Ile Lys Gly Glu His Pro Gly Leu Ser Ile Gly Asp Val Ala Lys Lys 115 120 125

Leu Gly Glu Met Trp Asn Asn Thr Ala Ala Asp Asp Lys Gln Pro Tyr 130 135 140

Glu Lys Lys Ala Ala Lys Leu Lys Glu Lys Tyr Glu Lys Asp Ile Ala 145 150 155 160

Ala Tyr Arg Ala Lys Gly Lys Pro Asp Ala Ala Lys Lys Gly Val Val 165 170 175

Lys Ala Glu Lys Ser Lys Lys Lys Glu Glu Glu Glu Asp Glu Glu 180 185 190

Asp Glu Glu Asp Glu Glu Glu Glu Glu Asp Glu Asp Glu Asp Glu Asp Glu 195 200 205

Glu Glu Asp Asp Asp Asp Glu 210 215

<210> 210

<211> 243

<212> PRT

<213> Homo sapiens

<400> 210

Met Ala Ala Ile Ala Ala Ser Glu Val Leu Val Asp Ser Ala Glu Glu 1 10 15

Gly Ser Leu Ala Ala Ala Ala Glu Leu Ala Ala Gln Lys Arg Glu Gln  $20 \hspace{1cm} 25 \hspace{1cm} 30 \hspace{1cm}$ 

Arg Leu Arg Lys Phe Arg Glu Leu His Leu Met Arg Asn Glu Ala Arg 35 40 45

Lys Leu Asn His Gln Glu Val Val Glu Glu Asp Lys Arg Leu Lys Leu 50 60

Pro Ala Asn Trp Glu Ala Lys Lys Ala Arg Leu Glu Trp Glu Leu Lys 65 70 75 80

Glu Glu Lys Lys Lys Glu Cys Ala Ala Arg Gly Glu Asp Tyr Glu 85 90 95

Lys Val Lys Leu Leu Glu Ile Ser Ala Glu Asp Ala Glu Arg Trp Glu 100 105 110

Arg Lys Lys Arg Lys Asn Pro Asp Leu Gly Phe Ser Asp Tyr Ala 115 120 125

Ala Ala Gln Leu Arg Gln Tyr His Arg Leu Thr Lys Gln Ile Lys Pro 130 135 140

Asp Met Glu Thr Tyr Glu Arg Leu Arg Glu Lys His Gly Glu Glu Phe 145 150 150 160

Phe Pro Thr Ser Asn Ser Leu Leu His Gly Thr His Val Pro Ser Thr 165 170 170 175

Glu Glu Ile Asp Arg Met Val Ile Asp Leu Glu Lys Gln Ile Glu Lys 180 185 190

Arg Asp Lys Tyr Ser Arg Arg Arg Pro Tyr Asn Asp Asp Ala Asp Ile 195 200 205

Asp Tyr Ile Asn Glu Arg Asn Ala Lys Phe Asn Lys Lys Ala Glu Arg 210 215 220

Phe Tyr Gly Lys Tyr Thr Ala Glu Île Lys Gln Asn Leu Glu Arg Gly 225 230 230 235

Thr Ala Val

<210> 211

<211> 479

<212> PRT

<213> Homo sapiens

<400> 211

Met Leu Gln Ile Asn Gln Met Phe Ser Val Gln Leu Ser Leu Gly Glu 1 10 15

Gln Thr Trp Glu Ser Glu Gly Ser Ser Ile Lys Lys Ala Gln Gln Ala 20 25 30

Val Ala Asn Lys Ala Leu Thr Glu Ser Thr Leu Pro Lys Pro Val Gln 35 40 45

Lys Pro Pro Lys Ser Asn Val Asn Asn Asn Pro Gly Ser Ile Thr Pro 50 60

Thr Val Glu Leu Asn Gly Leu Ala Met Lys Arg Gly Glu Pro Ala Ile 65 70 80

Tyr Arg Pro Leu Asp Pro Lys Pro Phe Pro Asn Tyr Arg Ala Asn Tyr 85 90 95

Asn Phe Arg Gly Met Tyr Asn Gln Arg Tyr His Cys Pro Val Pro Lys 100 105 110

Ile Phe Tyr Val Gln Leu Thr Val Gly Asn Asn Glu Phe Phe Gly Glu 115 120 125

Gly Lys Thr Arg Gln Ala Ala Arg His Asn Ala Ala Met Lys Ala Leu 130 135 140

Gln Ala Leu Gln Asn Glu Pro Ile Pro Glu Arg Ser Pro Gln Asn Gly 145  $\phantom{\bigg|}$  150  $\phantom{\bigg|}$  150  $\phantom{\bigg|}$  155  $\phantom{\bigg|}$  160

Glu Ser Gly Lys Asp Met Asp Asp Asp Lys Asp Ala Asn Lys Ser Glu 165 170 175

Ile Ser Leu Val Phe Glu Ile Ala Leu Lys Arg Asn Met Pro Val Ser 180  $$185\$ 

- Phe Glu Val Ile Lys Glu Ser Gly Pro Pro His Met Lys Ser Phe Val
- Thr Arg Val Ser Val Gly Glu Phe Ser Ala Glu Gly Glu Gly Asn Ser 210 215 220
- Lys Lys Leu Ser Lys Lys Arg Ala Ala Thr Thr Val Leu Gln Glu Leu 225 230 235 240
- Lys Lys Leu Pro Pro Leu Pro Val Val Glu Lys Pro Lys Leu Phe Phe 245  $\phantom{0}250$   $\phantom{0}255$
- Lys Lys Arg Pro Lys Thr Ile Val Lys Ala Gly Pro Glu Tyr Gly Gln  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$
- Gly Met Asn Pro Ile Ser Arg Leu Ala Gln Ile Gln Gln Ala Lys Lys  $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285$
- Glu Lys Glu Pro Asp Tyr Val Leu Leu Ser Glu Arg Gly Met Pro Arg 290 295 300
- Arg Arg Glu Phe Val Met Gln Val Lys Val Gly Asn Glu Val Ala Thr 305 310 315 320
- Gly Thr Gly Pro Asn Lys Lys Ile Ala Lys Lys Asn Ala Ala Glu Ala 325 330 335
- Met Leu Gun Leu Gly Tyr Lys Ala Ser Thr Asn Leu Gln Asp Gln 340 345 350
- Leu Glu Lys Thr Gly Glu Asn Lys Gly Trp Ser Gly Pro Lys Pro Gly 355 360 365
- Phe Pro Glu Pro Thr Asn Asn Thr Pro Lys Gly Ile Leu His Leu Ser 370 375 380
- Pro Asp Val Tyr Gln Glu Met Glu Ala Ser Arg His Lys Val Ile Ser 385  $\phantom{\bigg|}390\phantom{\bigg|}395\phantom{\bigg|}400\phantom{\bigg|}$
- Gly Thr Thr Leu Gly Tyr Leu Ser Pro Lys Asp Met Asn Gln Pro Ser 405 410 415
- Ser Ser Phe Phe Ser Ile Ser Pro Thr Ser Asn Ser Ser Ala Thr Ile 420 425 430
- Ala Arg Glu Leu Leu Met Asn Gly Thr Ser Ser Thr Ala Glu Ala Ile 435 440 445
- Gly Leu Lys Gly Ser Ser Pro Thr Pro Pro Cys Ser Pro Val Gln Pro 450 455 460
- Ser Lys Gln Leu Glu Tyr Leu Ala Arg Ile Gln Gly Phe Gln Val 465 470 475

## (19) World Intellectual Property Organization International Bureau





### (43) International Publication Date 17 October 2002 (17.10.2002)

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(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,

#### Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

## Published:

with international search report

(88) Date of publication of the international search report: 27 February 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROSTATE CANCER EXPRESSION PROFILES

(57) Abstract: The present invention relates to all facets of novel polynucleotides, the polypeptides they encode, antibodies and specific binding partners thereto, and their applications to research, diagnosis, drub discovery, therapy, clinical medicine, forensic science and medicine, etc. The polynucleotides are differentially-regulated in prostate cancer and are therefore useful in variety of ways, including, but not limited to, as molecular markers, as drug targets, and for detecting, diagnosing, staging, monitoring, prognosticating, preventing or treating, determining predisposition to, etc., diseases and conditions, to prostate cancer.



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/10824

A. CLASSIFICATION OF SUBJECT MATTER							
IPC(7) : ¢12N 15/12, 15/11; C12Q 1/68; G01N 33/53, 33/48; C07K 16/00; A01N 43/04; A61K 38/00; A01K 67/00							
	US CL : \$36/23.5, 23.1; 435/6, 7.1, 91.2; 514/12, 44; 530/387.1; 800/9						
	According to International Patent Classification (IPC) or to both national classification and IPC  B. FIELDS SEARCHED						
11 5 - 5	cumentation searched (classification system followed 36/23.5, 23.1; 435/6, 7.1, 91.2; 514/12, 44; 530/387	by classification symbols)					
0.5 5	30/23.3, 23.1, 433/0, 7.1, 91.2, 314/12, 44, 330/36/	.1; 800/9					
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Documentati	on searched other than minimum documentation to the	e extent that such documents are included	in the fields searched				
Electronic de	Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)						
	nucleic acid and amino acid sequence databases): SEO		caren terms used)				
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C. DOC	UMENTS CONSIDERED TO BE RELEVANT		<del></del>				
Category *		managed of the relevant managed	Dalaman a dalam Na				
X	Citation of document, with indication, where ap HORREVOETS et al, Vascular endothelial genes th		Relevant to claim No.				
•	factor alpha in vitro are expressed in atherosclerotic		26				
	apoptosis protein-1, stamin, and two novel genes, I						
	pages 3418-3431, see entire document.	,,,,,,,					
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Burthe	r documents are listed in the continuation of Box C.	Sag patent family apper					
	Special categories of cited documents:	See patent family annex.					
i		priority date and not in conflict with	the application but cited to				
"A" document	at defining the general state of the art which is not considered to ricular relevance	understand the principle or theory u	nderlying the invention				
•		"X" document of particular relevance; th					
date	pplication or patent published on or after the international filing	considered novel or cannot be consi step when the document is taken alo					
"L" documen	it which may throw doubts on priority claim(s) or which is cited	"Y" document of particular relevance; th	a delegat invention connect be				
to establ	ish the publication date of another citation or other special reason	considered to involve an inventive a	tep when the document is				
(as speci	lice)	combined with one or more other su combination being obvious to a per					
"O" documen	"O" document referring to an oral disclosure, use, exhibition or other means						
"P" document published prior to the international filing date but later than the							
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Date of the actual completion of the international search  15 July 2002 (15.07.2002)  Name and mailing address of the ISA/US  Commissioner of Patents and Trademarks  Box PCT  Date of mailing of the international search report  Authorized officer  Facility Bell  Howe for							
15 July 2002 (15.07.2002)							
Name and mailing address of the ISA/US  Authorized officer  Authorized officer							
Bo	mmissioner of Patents and Trademarks	James Martinell Sell - Nauros fr					
Washington, D.C. 20231							
Facsimile No. (703)305-3230 Telephone No. (703) 308-0196							

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

International application No.

PCT/US02/10824

Box 1	Obser	rvations v	where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This i	nternatio	onal report	t has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	$\boxtimes$	because th	s.: 23 and 25 sey relate to subject matter not required to be searched by this Authority, namely: s and 25 are drawn to displays of information.
2.	$\boxtimes$	such an ex	s.:  ney relate to parts of the international application that do not comply with the prescribed requirements to keep that no meaningful international search can be carried out, specifically:  ne claims depends from a plurality of other claims and not in the alternative.
3.	6.4(a).		os.: 2,5,8 and 17 hey are dependent claims and are not drafted in accordance with the second and third sentences of Rule
Box	II Ob	servation	s where unity of invention is lacking (Continuation of Item 2 of first sheet)
		ional Searc ontinuation	ching Authority found multiple inventions in this international application, as follows: n Sheet
1. 2. 3.		As all se payment As only	quired additional search fees were timely paid by the applicant, this international search report covers all le claims.  archable claims could be searched without effort justifying an additional fee, this Authority did not invite of any additional fee.  some of the required additional search fees were timely paid by the applicant, this international search wers only those claims for which fees were paid, specifically claims Nos.:
4.		is restric Sheet	ired additional search fees were timely paid by the applicant. Consequently, this international search report ted to the invention first mentioned in the claims; it is covered by claims Nos.: Please See Continuation
Kem	iark on	Protest	The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

1		International application No.			
INTE	RNATIONAL SEARCH REPORT				
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BOX II. OBSERVA	TIONS WHERE UNITY OF INVENTION IS LAC	CKING			
This application contain	ins the following inventions or groups of inventions which a	re not so linked as to form a single general			
be paid.	PCT Rule 13.1. In order for all inventions to be examine	ed, the appropriate additional examination fees must			
oc patu.	į				
The claims are directe	d to 211 independent, distinct, and unrelated nucleic acid a	nd polypeptide sequences that do not share a			
common technical feat	ure. Accordingly, there are 211 Groups of inventions, one	for each independent, distinct, and unrelated			
nucleic acid and polyp	eptide sequence.				
		Į.			
The inventions listed a	s Groups1-211 do not relate to a single general inventive co	oncept under PCT Rule 13.1 because, under PCT			
kme 13.2, they lack the	ne same or corresponding special technical features for the	following reasons: the application does not disclose			
now any or the sequen	ces relates to any of the other sequences.				
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Continuation of Bo	x II Item 4:				
1, 3, 4, 7, 9-16, 18-22	2, 24, and 26 insofar as they relate to SEQ ID NOs: 2 and 1	41.			
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